527 Rec'd P 13 NOV 2000

EXPRESS MAIL CERTIFICATE

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231. 09/700354

Typed or Printed Name	Mathew Ohs	**Express Mail No.**	EL 563 650 845 US
Signature		**Date**	November 13, 2000

Form PTO-1390 (REV 10-94)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: IRVN-007CIP2

U.S. APPLICATION NO.:

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT US99/10793	May 14, 1999	May 14, 1998

TITLE OF INVENTION: Factors Affecting Tumor Necrosis Factor Receptor Releasing Enzyme Activity

APPLICANT(S) FOR DO/EO/US: The Regents of the University of California; EATAMAGA Tetsuya.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. X This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ___ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. X This express request to begin examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and the PCT Articles 22 and 39(1).

4. X A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. X A copy of the International Application as filed (35 U.S.C. 371(c)(2)):
   a. ___ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. X has been transmitted by the International Bureau.
   c. ___ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ___ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. X Amendments to the claims of the International Application under PCT Article 19 (37 U.S.C. 371(c)(3)):
   a. X are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ___ have been transmitted by the International Bureau.
   c. ___ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ___ have not been made and will not be made.

8. ___ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. X An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). **(SIGNED)**

10. ___ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern other document(s) or information included:

11. ___ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ___ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. X A **FIRST** preliminary amendment.
    ___ A **SECOND** or **SUBSEQUENT** preliminary amendment.

14. ___ A substitute specification.

15. ___ A change of power of attorney and/or address letter.

16. ___ Other items or information:

U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 09/700354	INTERNATIONAL APPLICATION NO. PCT US99/10793	529 Rec'd PCT/PTC 13 NOV 2000 ATTORNEY'S DOCKET NUMBER IRVN-007CIP2

17. X The following fees are submitted:

Basic National Fee (37 CFR 1.492(a)(1)-(5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and international search report not prepared by the EPO or JPO	$970.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search report prepared by the EPO or JPO	$840.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$690.00		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$670.00		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$ 96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =		$840.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than __20 __30 months from the earliest claimed priority date (37 CFR 1.492(e)).		$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	20 - 20 =	00	X $18.00	$	
Independent Claims	06 - 03 =	03	X $78.00	$234.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	$	
TOTAL OF ABOVE CALCULATIONS =				$	
Reduction of ½ for filing by small entity, if applicable. (Note 37 CFR 1.9, 1.27, 1.28)				$537.00	
SUBTOTAL =				$537.00	
Processing Fee of **$130.00** for furnishing the English translation later than __20 __30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$537.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property.				$	
TOTAL FEES ENCLOSED =				$537.00	
				Amount to be: refunded	$
				charged	$537.00

a. __ A check in the amount of $__* to cover the above fees is included.

b. X Please charge my Deposit Account No. 50-0815 in the amount of $ 537.00 to cover the above fees.

c. X The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-0815.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Carol L. Francis
SIGNATURE

SEND ALL CORRESPONDENCE TO

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
(650) 327-3400 Telephone
(650) 327-3231 Facsimile

NAME: Carol L. Francis

36,513
REGISTRATION NUMBER

F:\DOCUMENT\IRVN (UC Irvine)\007cip2\nat phase application transmittal.wpd

EXPRESS MAIL CERTIFICATE			
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.			
Typed or Printed Name	Mathew Otts	**Express Mail No.**	EL 563 650 845 US
Signature		**Date**	November 13, 2000

PRELIMINARY AMENDMENT Address to: Commissioner for Patents Washington, D.C. 20231		
	Attorney Docket	IRVN-007CIP2 (UC 96-367-4)
	First Named Inventor	Gatanaga, et al.
	Application Number	N/A
	Filing Date	Herewith
	Group Art Unit	N/A
	Examiner Name	N/A
	Title	Factors Affecting Tumor Necrosis factor Receptor Releasing Enzyme Activity

Sir:

Prior to the examination on the merits of the above-referenced application, please amend the application as follows.

AMENDMENTS

In The Claims:

Cancel claims 1-36 without prejudice.

Add the following new claims:

-- 37. (New) An isolated polypeptide having at least one of the following properties:

a) the polypeptide comprises at least 10 consecutive amino acid residues encoded in any of SEQ ID NOs:8, 9, 1-3, 5-6, or 10; or

b) the polypeptide comprises at least 15 consecutive amino acids that are at least 80% identical to a sequence encoded in any of SEQ ID NOs:8, 9, 1-3, 5-6, or 10.

38. (New) The polypeptide of claim 37, having at least one of the following properties:

a) the polypeptide comprises at least 10 consecutive amino acid residues contained in SEQ ID NOs: 147-149, 151, or 153-154;

b) the polypeptide comprises at least 15 consecutive amino acids that are at least 80% identical to a sequence contained in SEQ ID NOS: 147-149, 151, or 153-154.

39. (New) The polypeptide of claim 37, which when incubated with COS-1 cells expressing TNF receptor, promotes enzymatic cleavage and release of the receptor.

40. (New) The polypeptide of claim 37, which is immunogenic for an antibody specific for a modulator of TRRE activity.

41. (New) The polypeptide of claim 37, which either:

a) lacks a membrane spanning sequence; or

b) is produced by a process comprising recombinant expression in a host cell followed by purification of the polypeptide from medium in which the cell is cultured.

42. (New) A method of producing the polypeptide according to any of claim 37, comprising:

a) culturing host cells genetically altered to express a polynucleotide comprising an encoding sequence for the polypeptide; and subsequently

b) purifying the polypeptide from the cells.

43. (New) The method of claim 42, comprising harvesting culture medium, and purifying the polypeptide from the culture medium by a process comprising affinity chromatography.

44. (New) An isolated antibody specific for a polypeptide according to claim 37.

45. (New) A method for producing the antibody according to claim 44, comprising immunizing a mammal or contacting an immunocompetent cell or particle with a polypeptide according to claim 37.

46. (New) An assay method for determining altered TRRE activity in a cell or tissue sample, comprising:

a) contacting the sample with a polynucleotide under conditions that permit the polynucleotide to hybridize specifically with nucleic acid that encodes a modulator of TRRE activity, if present in the sample; and

b) determining polynucleotide that has hybridized as a result, as a measure of altered TRRE activity in the sample;

wherein the polynucleotide has at least one of the following properties:

i) the polynucleotide comprises a nucleotide sequence contained in SEQ ID NOs:1-10;

ii) the polynucleotide comprises a nucleotide sequence of at least 30 consecutive nucleotides contained in SEQ ID NOs:1-10;

iii) the polynucleotide comprises a nucleotide sequence of at least 50 consecutive nucleotides at least 90% identical to a sequence contained in SEQ ID NOs:1-10; or

iv) the polynucleotide is capable of hybridizing specifically to a nucleotide sequence contained in SEQ ID NOs:1-10 under stringent conditions.

47. (New) The assay method of claim 46, wherein the polynucleotide comprises a nucleotide sequence of at least 30 consecutive nucleotides contained in SEQ ID NOs:1-10.

48. (New) An assay method for determining altered expression of a modulator of TRRE activity in a cell or tissue sample, comprising:

a) contacting the sample with the antibody of claim 44 under conditions that permit the antibody to bind the modulator if present in the sample, thereby forming an antibody-antigen complex; and

b) determining any complex formed as a measure of altered expression of the modulator.

49. (New) A method for assessing a disease condition associated with altered TRRE activity in a subject, comprising determining altered expression of a TRRE modulator according to claim 46, and then correlating the extent of alteration with the disease condition.

50. (New) A method for decreasing signal transduction from a cytokine into a cell, comprising contacting the cell with a polypeptide having at least one of the following properties:

a) the polypeptide comprises at least 10 consecutive amino acid residues encoded in any of SEQ ID NOs:1-10; or

b) the polypeptide comprises at least 15 consecutive amino acids that are at least 80% identical to a sequence encoded in any of SEQ ID NOs:1-10.

51. (New) A method for increasing signal transduction from a cytokine into a cell, comprising contacting the cell with an antibody according to claim 44.

52. (New) The method of claim 50, wherein the cytokine is TNF.

53. (New) A method of screening polynucleotides for an ability to modulate TRRE activity, comprising:

a) providing cells that express both TRRE and the TNF-receptor;

b) genetically altering the cells with the polynucleotides to be screened;

c) cloning the cells genetically altered; and

d) identifying clones that enzymatically release the receptor at an altered rate.

54. (New) A pharmaceutical composition comprising a polynucleotide in a pharmaceutically compatible excipient, wherein the polynucleotide has at least one of the following properties:

a) the polynucleotide comprises a nucleotide sequence contained in SEQ ID NOs:1-10;

b) the polynucleotide comprises a nucleotide sequence of at least 30 consecutive nucleotides contained in SEQ ID NOs:1-10;

c) the polynucleotide comprises a nucleotide sequence of at least 50 consecutive nucleotides at

least 90% identical to a sequence contained in SEQ ID NOs:1-10;

d) the polynucleotide is capable of hybridizing specifically to a nucleotide sequence contained in SEQ ID NOs:1-10 under stringent conditions; or

e) the polynucleotide comprises a nucleotide sequence that encodes at least 10 consecutive amino acids encoded in SEQ ID NOs:1-10.

55. (New) A pharmaceutical composition comprising a polypeptide in a pharmaceutically compatible excipient, wherein the polypeptide has at least one of the following properties:

a) the polypeptide comprises at least 10 consecutive amino acid residues encoded in any of SEQ ID NOs:1-10; or

b) the polypeptide comprises at least 15 consecutive amino acids that are at least 80% identical to a sequence encoded in any of SEQ ID NOs:1-10.

56. (New) A pharmaceutical composition comprising an antibody according to claim 44 in a pharmaceutically compatible excipient.--

REMARKS

Claims 37-56 are pending after entry of the amendments above.

Claims 1-36 are canceled without prejudice to renewal, without intent to abandon any subject matter therein, and without acquiescing to any rejection which may have been applied. Applicants expressly reserve the right to pursue the subject matter of the canceled claims in a continuing application.

Support for new claims 37-43 is found in, for example, claims 7-14 as originally filed.

Support for new claims 44-45 is found in, for example, claims 16 and 17as originally filed.

Support for new claims 46-47 is found in, for example, claims 18, 3, 4, and 5 as originally filed.

Support for new claim 48 is found in, for example, claim 19 as originally filed.

Support for new claim 49 is found in, for example, claim 20 as originally filed.

Support for new claim 50 is found in, for example, claims 21, 9, and 10 as originally filed.

Support for new claims 51, 52 and 53 is found in, for example, claims 22-24 as originally filed.

Support for new claim 54 is found in, for example, claims 2-6 and 27 as originally filed, as well as in the specification at page 26, lines 3-28 and page 27, lines 16-30.

Support for new claim 55 is found in, for example, claims 29 and 7-14 as originally filed, as well as in the specification at page 25, line 26 to page 26, line 2and page 27, lines 16-30.

Support for new claims 56 is found in, for example, claim 28 as originally filed as well as in the specification at page 21, lines 5-9.

No new matter is added.

CONCLUSION

Applicants respectfully submit that the claims are in form for allowance, early notice of which is requested. If, in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 327-3400.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: November 13, 2007

By: _____
Carol L. Francis
Registration No. 36,513

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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Our Docket: FP-UC 3668

PATENT COOPERATION TREATY
IN THE INTERNATIONAL BUREAU OF WIPO

In re International Application No. PCT/US99/10793	)
Applicant: The Regents of the University of California, et al.	)
Filed: 14 May 1999	)
Entitled: FACTORS AFFECTING TUMOR NECROSIS FACTOR RECEPTOR RELEASING ENZYME ACTIVITY	)

International Bureau of WIPO
34, chemin des Colombettes
1221 Geneva 20
Switzerland

LETTER

Sir:

Pursuant to PCT Article 19(1), and responsive to the International Search Report dated December 3, 1999, Applicant respectfully requests that the following amendments and remarks be considered and that the Substitute page submitted herewith be entered for examination.

AMENDMENTS

Applicant respectfully requests replacement of original page 99 with the enclosed substitute page 99. The status of the claims is as follows:

Claims 1 to 32 are unchanged.

New claims 33 to 35 have been added, as follows:

--33. The polynucleotide according to any of claims 1-5, wherein said nucleotide sequence is not contained in any of the sequences of the following GenBank Accession Nos: AJ003355, AA806165; AI002979; T33896; U52522; AA779203; C06247; AA707194; AA599596; 5453538; U13369; and J03528.

34. The polypeptide according to any of claims 7-10, the sequence of which is not completely encoded by a polynucleotide sequence contained in any of the sequences of the following GenBank Accession Nos: AJ003355, AA806165; AI002979; T33896; U52522; AA779203; C06247; AA707194; AA599596; 5453538; U13369; and J03528.

35. The polynucleotide according to claim 15, the sequence of which is not contained in any of the sequences of the following GenBank Accession Nos: AJ003355, AA806165; AI002979; T33896; U52522; AA779203; C06247; AA707194; AA599596; 5453538; U13369; and J03528.--

REMARKS

The GenBank Accession Numbers recited in new claims 33 to 35 relate to items cited in the International Search Report.

CONCLUSION

The Examiner is invited to contact the undersigned agent or Cathryn Campbell if there are any questions relating to the subject application.

Respectfully submitted,

Date: 11/13/00

Melanie K. Webster
Registration No. 45,201
(Tel) 858.535.9001
(Fax) 858.535.8949

CAMPBELL & FLORES LLP
4370 La Jolla Village Drive
Suite 700
San Diego, California 92122

FACTORS AFFECTING TUMOR NECROSIS FACTOR RECEPTOR RELEASING ENZYME ACTIVITY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the priority benefit of U.S. application 09/081,385, filed May 14, 1998, pending. For purposes of prosecution in the U.S., the priority application is hereby incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

This invention relates generally to the field of signal transduction between cells, via cytokines and their receptors. More specifically, it relates to enzymatic activity that cleaves and releases the receptor for TNF found on the cell surface, and the consequent biological effects. Certain embodiments of this invention are compositions that affect such enzymatic activity, and may be included in medicaments for disease treatment.

BACKGROUND OF THE INVENTION

Cytokines play a central role in the communication between cells. Secretion of a cytokine from one cell in response to a stimulus can trigger an adjacent cell to undergo an appropriate biological response — such as stimulation, differentiation, or apoptosis. It is hypothesized that important biological events can be influenced not only by affecting cytokine release from the first cell, but also by binding to receptors on the second cell, which mediates the subsequent response. The invention described in this patent application provides new compounds for affecting signal transduction from tumor necrosis factor.

The cytokine known as tumor necrosis factor (TNF or TNF-α) is structurally related to lymphotoxin (LT or TNF-β). They have about 40 percent amino acid sequence homology (Old, *Nature* 330:602-603, 1987). These cytokines are released by macrophages, monocytes and natural killer cells and

play a role in inflammatory and immunological events. The two cytokines cause a broad spectrum of effects both in vitro and in vivo, including: (i) vascular thrombosis and tumor necrosis; (ii) inflammation; (iii) activation of macrophages and neutrophils; (iv) leukocytosis; (v) apoptosis; and (vi) shock. TNF has been associated with a variety of disease states including various forms of cancer, arthritis, psoriasis, endotoxic shock, sepsis, autoimmune diseases, infections, obesity, and cachexia. TNF appears to play a role in the three factors contributing to body weight control: intake, expenditure, and storage of energy (Rothwell, *Int. J. Obesity* 17:S98-S101, 1993). In septicemia, increased endotoxin concentrations appear to raise TNF levels (Beutler et al. *Science* 229:869-871, 1985).

Attempts have been made to alter the course of a disease by treating the patient with TNF inhibitors, with varying degrees of success. For example, the TNF inhibitor dexanabinol provided protection against TNF mediated effects following traumatic brain injury (Shohami et al. *J. Neuroimmun.* 72:169-77, 1997). Some improvement in Crohn's disease was afforded by treatment with anti-TNF antibodies (Neurath et al., *Eur. J. Immun.* 27:1743-50, 1997).

Human TNF and LT mediate their biological activities by binding specifically to two distinct glycoprotein plasma membrane receptors (55 kDa and 75 kDa in size, known as p55 and p75 TNF-R, respectively). The two receptors share 28 percent amino acid sequence homology in their extracellular domains, which are composed of four repeating cysteine-rich regions (Tartaglia and Goeddel, *Immunol. Today* 13:151-153, 1992). However, the receptors lack significant sequence homology in their intracellular domains, and mediate different intracellular responses to receptor activation. In accordance with the different activities of TNF and LT, most human cells express low levels of both TNF receptors: about 2,000 to 10,000 receptors per cell (Brockhaus et al., *Proc. Natl. Acad. Sci.* USA *87:3127-3131,* 1990).

Expression of TNF receptors on both lymphoid and non-lymphoid cells can be influenced experimentally by many different agents, such as bacterial lipopolysaccharide (LPS), phorbol myristate acetate (PMA; a protein kinase C

activator), interleukin-1 (IL-1), interferon-gamma (IFN-γ) and IL-2 (Gatanaga et al. *Cell Immunol.* 138:1-10, 1991; Yui et al. *Placenta* 15:819-835, 1994). It has been shown that complexes of human TNF bound to its receptor are internalized from the cell membrane, and then the receptor is either degraded or recycled (Armitage, *Curr. Opin. Immunol.* 6:407-413, 1994). It has been proposed that TNF receptor activity can be modulated using peptides that bind intracellularly to the receptor, or which bind to the ligand binding site, or that affect receptor shedding. See for example patent publications WO 95/31544, WO 95/33051, WO 96/01642, and EP 568 925.

TNF binding proteins (TNF-BP) have been identified at elevated levels in the serum and urine of febrile patients, patients with renal failure, and cancer patients, and even certain healthy individuals. Human brain and ovarian tumors produced high serum levels of TNF-BP These molecules have been purified, characterized, and cloned (Gatanaga et al., *Lymphokine Res.* 9:225-229, 1990a; Gatanaga et al., *Proc. Natl. Acad. Sci USA* 87:8781-8784, 1990b). Human TNF-BP consists of 30 kDa and 40 kDa proteins which are identical to the N-terminal extracellular domains of p55 and p75 TNF receptors, respectively (US Patent No. 5,395,760; EP 418,014). Such proteins have been suggested for use in treating endotoxic shock. Mohler et al. *J. Immunol.* 151:1548–1561, 1993

There are several mechanisms possible for the production of secreted proteins resembling membrane bound receptors. One involves translation from alternatively spliced mRNAs lacking transmembrane and cytoplasmic regions. Another involves proteolytic cleavage of the intact membrane receptors, followed by shedding of the cleaved receptor from the cell. The soluble form of p55 and p75 TNF-R do not appear to be generated from mRNA splicing, since only full length receptor mRNA has been detected in human cells *in vitro* (Gatanaga et al., 1991). Carboxyl-terminal sequencing and mutation studies on human p55 TNF-R indicates that a cleavage site may exist between residues Asn 172 and Val 173 (Gullberg et al. *Eur. J. Cell. Biol.* 58:307-312, 1992).

There are reports that a specific metalloprotease inhibitor, TNF-α protease inhibitor (TAPI) blocks the shedding of soluble p75 and p55 TNF-R (Crowe et al.

J. Exp. Med. 181:1205-1210, 1995; Mullberg et al. *J. Immunol.* 155:5198-5205, 1995). The processing of pro-TNF on the cell membrane to release the TNF ligand appears to be dependent on a matrix metalloprotease like enzyme (Gearing et al. *Nature* 370:555-557, 1994). This is a family of structurally related matrix-degrading enzymes that play a major role in tissue remodeling and repair associated with development and inflammation (Birkedal-Hansen et al. *Crit. Rev. Oral Biol. Med.* 4:197–250, 1993). The enzymes have Zn^{2+} in their catalytic domains, and Ca^{2+} stabilizes their tertiary structure significantly.

In European patent application EP 657536A1, Wallach et al. suggest that it would be possible to obtain an enzyme that cleaves the 55,000 kDa TNF receptor by finding a mutated form of the receptor that is not cleaved by the enzyme, but still binds to it. The only proposed source for the enzyme is a detergent extract of membranes for cells that appear to have the protease activity. If it were possible to obtain an enzyme according to this scheme, then the enzyme would presumably comprise a membrane spanning region. The patent application does not describe any protease that was actually obtained.

In a previous patent application in the present series (International Patent Publication WO 9820140), methods are described for obtaining an isolated enzyme that cleaves both the p55 and p75 TNF-R from cell surfaces. A convenient source is the culture medium of cells that have been stimulated with phorbol myristate acetate (PMA). The enzyme activity was given the name TRRE (TNF receptor releasing enzyme). In other studies, TRRE was released immediately upon PMA stimulation, indicating that it is presynthesized in an inactive form to be rapidly converted to the active form upon stimulation. Evidence for direct cleavage of TNF-R is that the shedding begins very quickly (~5 min) with maximal shedding within 30 min. TRRE is specific for the TNF-R, and does not cleave IL-1 receptors, CD30, ICAM-1 or CD11b. TRRE activity is enhanced by adding Ca^{++} or Zn^{++}, and inhibited by EDTA and phenantroline.

Given the involvement of TNF in a variety of pathological conditions, it is desirable to obtain a variety of factors that would allow receptor shedding to be

modulated, thereby controlling the signal transduction from TNF at a disease site.

SUMMARY OF THE INVENTION

This disclosure provides new compounds that promote enzymatic cleavage and release of TNF receptors from the cell surface. Nine new DNA clones have been selected after repeat screening in an assay that tests the ability to enhance receptor release. The polynucleotide sequences of this invention and the proteins encoded by them have potential as diagnostic aids, and therapeutic compounds that can be used to adjust TNF signal transduction in a beneficial way.

One embodiment of the invention is an isolated polynucleotide comprising a nucleotide sequence with the following properties: a) the sequence is expressed at the mRNA level in Jurkat T cells; b) when COS-1 cells expressing TNF-receptor are genetically transformed to express the sequence, the cells have increased enzymatic activity for cleaving and releasing the receptor. If a polynucleotide sequence is expressed in Jurkat cells, then it can be found in the Jurkat cell expression library deposited with the ATCC (Accession No. TIB-152). It is recognized that the polynucleotide can be obtained from other cell lines, or produced by recombinant techniques.

Included are polynucleotides in which the nucleotide sequence is contained in any of SEQ. ID NOS:1-10. Also embodied are polynucleotides comprising at least 30 and preferably more consecutive nucleotides in said nucleotide sequence, or at least 50 consecutive nucleotides that are homologous to said sequence at a significant level, preferably at the 90% level or more. Also included antisense and ribozyme polynucleotides that inhibit the expression of a TRRE modulator.

Another embodiment of the invention is isolated polypeptides comprising an amino acid sequence encoded by a polynucleotide of this invention. Non-limiting examples are sequences shown in SEQ. ID NOS: 147-158. Fragments

and fusion proteins are included in this invention, and preferably comprise at least 10 consecutive residues encoded by a polynucleotide of this invention, or at least 15 consecutive amino acids that are homologous at a significant level, preferably at least 80%. Preferred polypeptides promote cleavage and release of TNF receptors from the cell surface, especially COS-1 cells genetically transformed to express TNF receptor. The polypeptides may or may not have a membrane spanning domain, and may optionally be produced by a process that involves secretion from a cell. Included are species homologs with the desired activity, and artificial mutants with additional beneficial properties.

Another embodiment of this invention is an antibody specific for a polypeptide of this invention. Preferred are antibodies that bind a TRRE modulator protein, but not other substances found in human tissue samples in comparable amounts.

Another embodiment of the invention is an assay method of determining altered TRRE activity in a cell or tissue sample, using a polynucleotide or antibody of this invention to detect the presence or absence of the corresponding TRRE modulator. The assay method can optionally be used for the diagnosis or evaluation of a clinical condition relating to abnormal TNF levels or TNF signal transduction.

Another embodiment of the invention is a method for increasing or decreasing signal transduction from a cytokine into a cell (including but not limited to TNF), comprising contacting the cell with a polynucleotide, polypeptide, or antibody of this invention.

A further embodiment of the invention is a method for screening polynucleotides for an ability to modulate TRRE activity. The method involves providing cells that express both TRRE and the TNF-receptor; genetically altering the cells with the polynucleotides to be screened; cloning the cells; and identifying clones with the desired activity.

Yet another embodiment of the invention is a method for screening substances for an ability to affect TRRE activity. This typically involves incubating cells expressing TNF receptor with a TRRE modulator of this

invention in the presence or absence of the test substance; and measuring the effect on shedding of the TNF receptor .

The products of this invention can be used in the preparation of a medicament for treatment of the human or animal body. The medicament contains a clinically effective amount for treatment of a disease such as heart failure, cachexia, inflammation, endotoxic shock, arthritis, multiple sclerosis, sepsis, and cancer. These compositions can be used for administration to a subject suspected of having or being at risk for the disease, optionally in combination with other forms of treatment appropriate for their condition.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic representation of plasmid pCDTR2. This plasmid expresses p75 TNF-R, the ~75 kDa form of the TNF receptor. PCMV stands for cytomegalovirus; BGHpA stands for bovine growth hormone polyadenylation signal.

Figure 2 is a line depicting the levels of p75 TNF-R detected on COS-1 cells genetically altered to express the receptor. Results from the transformed cells, designated C75R (●, upward swooping line) is compared with that from the parental COS-1 cells (■, baseline). The receptor number was calculated by Scatchard analysis (inset).

Figure 3 is a survival graph, showing that TRRE decreases mortality in mice challenged with lipopolysaccharide (LPS) to induce septic peritonitis. (◆) LPS alone; (■) LPS plus control buffer; (●) LPS plus TRRE (2,000 U); (▲) LPS plus TRRE (4,000 U).

Figure 4 is a half-tone reproduction of a bar graph, showing the effect of 9 new clones on TRRE activity on C75R cells (COS-1 cells transfected to express the TNF-receptor. Each of the 9 clones increases TRRE activity by over 2-fold.

Figure 5 is a survival graph, showing the ability of 4 new expressed to save mice challenged with LPS. (◆) saline; (■) BSA; (△) Mey-3 (100 μg); (X) Mey-3 (10 μg); (*) Mey-5 (10 μg); (●) Mey-8 (10 μg).

DETAILED DESCRIPTION OF THE INVENTION

It has been discovered that certain cells involved in the TNF transduction pathway express enzymatic activity that causes TNF receptors to be shed from the cell surface. Enzymatic activity for cleaving and releasing TNF receptors has been given the designation TRRE. Phorbol myristate acetate induces release of TRRE from cells into the culture medium. An exemplary TRRE protein had been purified from the supernatant of TNF-1 cells (Example 2). The protease bears certain hallmarks of the metalloprotease family, and is released rapidly from the cell upon activation.

In order to elucidate the nature of this protein, functional cloning was performed. Jurkat cells were selected as being a good source of TRRE. The cDNA from a Jurkat library was expressed, and cell supernatant was tested for an ability to release TNF receptors from cell surfaces. Cloning and testing of the expression product was conducted through several cycles, and nine clones were obtained that more than doubled TRRE activity in the assay (Figure 4). At the DNA level, all 9 clones had different sequences.

Protein expression products from the clones have been tested in a lipopolysaccharide animal model for sepsis. Protein from three different clones successfully rescued animals from a lethal dose of LPS (Figure 5). This points to an important role for these molecules in the management of pathological conditions mediated by TNF.

The number of new TRRE promoting clones obtained from the expression library was surprising. The substrate specificity of the TRRE isolated in Example 2 distinguishes the 75 kDa and 55 kDa TNF receptors from other cytokine receptors and cell surface proteins. There was little reason beforehand to suspect that cells might have nine different proteases for the TNF receptor. It is possible that one of the clones encodes the TRRE isolated in Example 2, or a related protein. It is possible that some of the other clones have proteolytic activity to cleave TNF receptors at the same site, or at another site that causes release of the soluble form from the cell. It is a hypothesis of this disclosure that some of the clones may not have proteolytic activity themselves, but play a role in promoting TRRE activity in a secondary fashion.

This possibility is consistent with the observations made, because there is an endogenous level of TRRE activity in the cells used in the assay. The cleavage assay involves monitoring TNF receptor release from C75 cells, which are COS-1 cells genetically altered to express p75 TNF-R. The standard assay is conducted by contacting the transformed cells with a fluid believed to contain TRRE. The level of endogenous TRRE activity is evident from the rate of spontaneous release of the receptor even when no exogenous TRRE is added (about 200 units). Accordingly, accessory proteins that promote TRRE activity would increase the activity measured in the assay. Many mechanisms of promotion are possible, including proteins that activate a zymogen form of TRRE, proteins that free TRRE from other cell surface components, or proteins that stimulate secretion of TRRE from inside the cell. It is not necessary to understand the mechanism in order to use the products of this invention in most of the embodiments described.

It is anticipated that several of the clones will have activity not just for promoting TNF receptor cleavage, but also having an effect on other surface proteins. To the extent that cleavage sequences or accessory proteins are shared between different receptors, certain clones would promote phenotypic change (such as receptor release) for the family of related substrates.

This disclosure provides polypeptides that promote TRRE activity, polynucleotides that encode such polypeptides, and antibodies that bind such peptides. The binding of TNF to its receptor mediates a number of biological effects. Cleavage of the TNF-receptor by TRRE diminishes signal transduction by TRRE. Potentiators of TRRE activity have the same effect. Thus, the products of this invention can be used to modulate signal transduction by cytokines, which is of considerable importance in the management of disease conditions that are affected by cytokine action. The products of this invention can also be used in diagnostic methods, to determine when signal transduction is being inappropriately affected by abnormal TRRE activity. The assay systems described in this disclosure provide a method for screening additional compounds that can influence TRRE activity, and thus the signal transduction from TNF.

Based on the summary of the invention, and guided by the illustrations in the example section, one skilled in the art will readily know what techniques to employ in the practice of the invention. The following detailed description is provided for the additional convenience of the reader.

Definitions and basic techniques

As used in this disclosure, "TRRE activity" refers to the ability of a composition to cleave and release TNF receptors from the surface of cells expressing them. A preferred assay is cleavage from transfected COS-1 cells, as described in Example 1. However, TRRE activity can be measured on any cells that bear TNF receptors of the 55 kDa or 75 kDa size. Other features of the TRRE enzyme obtained from PMA induction of THP-1 cells (exemplified in Example 2) need not be a property of the TRRE activity measured in the assay.

Unit activity of TRRE is defined as 1 pg of soluble p75 TNF-R released from cell surface in a standard assay, after correction for spontaneous release. The measurement of TRRE activity is explained further in Example 1.

A "TRRE modulator" is a compound that has the property of either increasing or decreasing TRRE activity for processing TNF on the surface of

cells. Those that increase TRRE activity may be referred to as TRRE promoters, and those that decrease TRRE activity may be referred to as TRRE inhibitors. TRRE promoters include compounds that have proteolytic activity for TNF-R, and compounds that augment the activity of TNF-R proteases. The nine polynucleotide clones described in Example 5, and their protein products, are exemplary TRRE promoters. Inhibitors of TRRE activity can be obtained using the screening assays described below.

The term "polynucleotide" refers to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Polynucleotides may have any three-dimensional structure, and may perform any function, known or unknown. The following are non-limiting examples of polynucleotides: a gene or gene fragment, exons, introns, (mRNA), ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, nucleic acid probes, and primers. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The term polynucleotide refers interchangeably to double-and single-stranded molecules. Unless otherwise specified or required, any embodiment of the invention described herein that is a polynucleotide encompasses both the double-stranded form, and each of two complementary single-stranded forms known or predicted to make up the double-stranded form

"Hybridization" refers to a reaction in which one or more polynucleotides react to form a complex that is stabilized via hydrogen bonding between the bases of the nucleotide residues. Hybridization reactions can be performed under conditions of different "stringency". Relevant conditions include temperature, ionic strength, and the presence of additional solutes in the reaction mixture such as formamide. Conditions of increasing stringency are 30°C. in 10X SSC (0.15M NaC1, 15 mM citrate buffer); 40°C. in 6X SSC; 50°C. in 6.X SSC 60°C. in 6X SSC, or at about 40°C. in 0.5X SSC, or at about 30°C. in 6.X. SSC containing 50% formamide. SDS and a source of fragmented DNA (such as salmon sperm) are typically also present during hybridization. Higher

stringency requires higher minimum complementarity between hybridizing elements for a stable hybridization complex to form. See "Molecular Cloning: A Laboratory Manual", Second Edition (Sambrook, Fritsch & Maniatis, 1989).

It is understood that purine and pyrimidine nitrogenous bases with similar structures can be functionally equivalent in terms of Watson-Crick base-pairing; and the inter-substitution of like nitrogenous bases, particularly uracil and thymine, or the modification of nitrogenous bases, such as by methylation, does not constitute a material substitution.

The percentage of sequence identity for polynucleotides or polypeptides is calculated by aligning the sequences being compared, and then counting the number of shared residues at each aligned position. No penalty is imposed for the presence of insertions or deletions, but are permitted only where required to accommodate an obviously increased number of amino acid residues in one of the sequences being aligned. When one of the sequences being compared is indicated as being "consecutive", then no gaps are permitted in that sequence during the comparison. The percentage identity is given in terms of residues in the test sequence that are identical to residues in the comparison or reference sequence.

As used herein, "expression" of a polynucleotide refers to the production of an RNA transcript. Subsequent translation into protein or other effector compounds may also occur, but is not required unless specified.

"Genetic alteration" refers to a process wherein a genetic element is introduced into a cell other than by mitosis or meiosis. The element may be heterologous to the cell, or it may be an additional copy or improved version of an element already present in the cell. Genetic alternation may be effected, for example, by transducing a cell with a recombinant plasmid or other polynucleotide through any process known in the art, such as electroporation, calcium phosphate precipitation, or contacting with a polynucleotide-liposome complex. Genetic alteration may also be effected, for example, by transduction or infection with a DNA or RNA virus or viral vector. It is preferable that the

genetic alteration is inheritable by progeny of the cell, but this is not generally required unless specified.

The terms "polypeptide", "peptide" and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation, such as conjugation with a labeling component.

A "fusion polypeptide" is a polypeptide comprising regions in a different position in the sequence than occurs in nature. The regions can normally exist in separate proteins and are brought together in the fusion polypeptide; they can normally exist in the same protein but are placed in a new arrangement in the fusion polypeptide; or they can be synthetically arranged. A "functionally equivalent fragment" of a polypeptide varies from the native sequence by addition, deletion, or substitution of amino acid residues, or any combination thereof, while preserving a functional property of the fragment relevant to the context in which it is being used. Fusion peptides and functionally equivalent fragments are included in the definition of polypeptides used in this disclosure.

It is understood that the folding and the biological function of proteins can accommodate insertions, deletions, and substitutions in the amino acid sequence. Some amino acid substitutions are more easily tolerated. For example, substitution of an amino acid with hydrophobic side chains, aromatic side chains, polar side chains, side chains with a positive or negative charge, or side chains comprising two or fewer carbon atoms, by another amino acid with a side chain of like properties can occur without disturbing the essential identity of the two sequences. Methods for determining homologous regions and scoring the degree of homology are described in Altschul et al. *Bull. Math. Bio.* 48:603-616, 1986; and Henikoff et al. *Proc. Natl. Acad. Sci. USA* 89:10915-10919, 1992. Substitutions that preserve the functionality of the polypeptide, or confer a new

and beneficial property (such as enhanced activity, stability, or decreased immunogenicity) are especially preferred.

An "antibody" (interchangeably used in plural form) is an immunoglobulin molecule capable of specific binding to a target, such as a polypeptide, through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term encompasses not only intact antibodies, but also antibody equivalents that include at least one antigen combining site of the desired specificity. These include but are not limited to enzymatic or recombinantly produced fragments antibody, fusion proteins, humanized antibodies, single chain variable regions, diabodies, and antibody chains that undergo antigen-induced assembly.

An "isolated" polynucleotide, polypeptide, protein, antibody, or other substance refers to a preparation of the substance devoid of at least some of the other components that may also be present where the substance or a similar substance naturally occurs or is initially obtained from. Thus, for example, an isolated substance may be prepared by using a purification technique to enrich it from a source mixture. Enrichment can be measured on an absolute basis, such as weight per volume of solution, or it can be measured in relation to a second, potentially interfering substance present in the source mixture. Increasing enrichments of the embodiments of this invention are increasingly more preferred. Thus, for example, a 2-fold enrichment is preferred, 10-fold enrichment is more preferred, 100-fold enrichment is more preferred, 1000-fold enrichment is even more preferred. A substance can also be provided in an isolated state by a process of artificial assembly, such as by chemical synthesis or recombinant expression.

A "host cell" is a cell which has been genetically altered, or is capable of being transformed, by administration of an exogenous polynucleotide.

The term "clinical sample" encompasses a variety of sample types obtained from a subject and useful in an in vitro procedure, such as a diagnostic test. The definition encompasses solid tissue samples obtained as a surgical removal, a pathology specimen, or a biopsy specimen, cells obtained from a

clinical subject or their progeny obtained from culture, liquid samples such as blood, serum, plasma, spinal fluid, and urine, and any fractions or extracts of such samples that contain a potential indication of the disease.

Unless otherwise indicated, the practice of the invention will employ conventional techniques of molecular biology, microbiology, recombinant DNA, and immunology, within the skill of the art. Such techniques are explained in the standard literature, such as: "Molecular Cloning: A Laboratory Manual", Second Edition (Sambrook, Fritsch & Maniatis, 1989), "Oligonucleotide Synthesis" (M. J. Gait, ed., 1984), "Animal Cell Culture" (R. I. Freshney, ed., 1987); the series "Methods in Enzymology" (Academic Press, Inc.); "Handbook of Experimental Immunology" (D. M. Weir & C. C. Blackwell, Eds.), "Gene Transfer Vectors for Mammalian Cells" (J. M. Miller & M. P. Calos, eds., 1987), "Current Protocols in Molecular Biology" (F. M. Ausubel et al., eds., 1987); and "Current Protocols in Immunology" (J. E. Coligan et al., eds., 1991). The reader may also choose to refer to a previous patent application relating to TRRE, International Patent Application WO 98020140.

For purposes of prosecution in the U.S., and in other jurisdictions where allowed, all patents, patent applications, articles and publications indicated anywhere in this disclosure are hereby incorporated herein by reference in their entirety.

Polynucleotides

Polynucleotides of this invention can be prepared by any suitable technique in the art. Using the data provided in this disclosure, sequences of less than ~50 base pairs are conveniently prepared by chemical synthesis, either through a commercial service or by a known synthetic method, such as the triester method or the phosphite method. A preferred method is solid phase synthesis using mononucleoside phosphoramidite coupling units (Hirose et al., *Tetra. Lett.* 19:2449-2452, 1978; U.S. Patent No. 4,415,732).

For use in antisense therapy, polynucleotides can be prepared by chemistry that produce more stable in pharmaceutical preparations. Non-limiting

examples include thiol-derivatized nucleosides (U.S. Patent 5,578,718), and oligonucleotides with modified backbones (U.S. Patent Nos. 5,541,307 and 5,378,825).

Polynucleotides of this invention can also be obtained by PCR amplification of a template with the desired sequence. Oligonucleotide primers spanning the desired sequence are annealed to the template, elongated by a DNA polymerase, and then melted at higher temperature so that the template and elongated oligonucleotides dissociate. The cycle is repeated until the desired amount of amplified polynucleotide is obtained (U.S. Patent Nos. 4,683,195 and 4,683,202). Suitable templates include the Jurkat T cell library and other human or animal expression libraries that contain TRRE modulator encoding sequences. The Jurkat T cell library is available from the American Type Culture Collection, 10801 University Blvd., Manassas VA 20110, U.S.A. (ATCC #TIB-152). Mutations and other adaptations can be performed during amplification by designing suitable primers, or can be incorporated afterwards by genetic splicing.

Production scale amounts of large polynucleotides are most conveniently obtained by inserting the desired sequence into a suitable cloning vector and reproducing the clone. Techniques for nucleotide cloning are given in Sambrook, Fritsch & Maniatis (supra) and in U.S. Patent No. 5,552,524. Exemplary cloning and expression methods are illustrated in Example 6.

Preferred polynucleotide sequences are 50%, 70%, 80% , 90%, or 100% identical to one of the sequences exemplified in this disclosure; in order if increasing preference. The length of consecutive residues in the identical or homologous sequence compared with the exemplary sequence can be about 15, 30, 50, 75, 100, 200 or 500 residues in order of increasing preference, up to the length of the entire clone. Nucleotide changes that cause a conservative substitution or retain the function of the encoded polypeptide (in terms of hybridization properties or what is encoded) are especially preferred substitutions.

The polynucleotides of this can be used to measure altered TRRE activity in a cell or tissue sample. This involves contacting the sample with the polynucleotide under conditions that permit the polynucleotide to hybridize specifically with nucleic acid that encodes a modulator of TRRE activity, if present in the sample, and determining polynucleotide that has hybridized as a result of step a). Specificity of the test can be provided in one of several ways. One method involves the use of a specific probe — a polynucleotide of this invention with a sequence long enough and of sufficient identity to the sequence being detected, so that it binds the target and not other nucleic acid that might be present in the sample. The probe is typically labeled (either directly or through a secondary reagent) so that it can be subsequently detected. Suitable labels include ^{32}P and ^{33}P, chemiluminescent and fluorescent reagents. After the hybridization reaction, unreacted probe is washed away so that the amount of hybridized probe can be determined. Signal can be amplified using branched probes (U.S. Patent No. 5,124,246). In another method, the polynucleotide is a primer for a PCR reaction. Specificity is provided by the ability of the paired probes to amplify the sequence of interest. After a suitable number of PCR cycles, the amount of amplification product present correlates with the amount of target sequence originally present in the sample.

Such tests are useful both in research, and in the diagnosis or assessment of a disease condition. For example, TNF activity plays a role in eliminating tumor cells (Example 4), and a cancer may evade the elimination process by activating TRRE activity in the diseased tissue. Hence, under some conditions, high expression of TRRE modulators may correlate with progression of cancer. Diagnostic tests are also of use in monitoring therapy, such as when gene therapy is performed to increase TRRE activity.

Polynucleotides of this invention can also be used for production of polypeptides and the preparation of medicaments, as explained below.

Polypeptides

Short polypeptides of this invention can be prepared by solid-phase chemical synthesis. The principles of solid phase chemical synthesis can be found in Dugas & Penney, Bioorganic Chemistry, Springer-Verlag NY pp 54-92 (1981), and U.S. Patent No. 4,493,795. Automated solid-phase peptide synthesis can be performed using devices such as a PE-Applied Biosystems 430A peptide synthesizer (commercially available from Applied Biosystems, Foster City CA).

Longer polypeptides are conveniently obtained by expression cloning. A polynucleotide encoding the desired polypeptide is operably linked to control elements for transcription and translation, and then transfected into a suitable host cell. Expression may be effected in procaryotes such as E. coli (ATCC Accession No. 31446 or 27325), eukaryotic microorganisms such as the yeast Saccharomyces cerevisiae, or higher eukaryotes, such as insect or mammalian cells. A number of expression systems are described in U.S. Patent No. 5 ,552,524. Expression cloning is available from such commercial services as Lark Technologies, Houston TX. The production of protein from 4 exemplary clones of this invention in insect cells is illustrated in Example 6. The protein is purified from the producing host cell by standard methods in protein chemistry, such as affinity chromatography and HPLC. Expression products are optionally produced with a sequence tag to facilitate affinity purification, which can subsequently be removed.

Preferred sequences are 40%, 60%, 80% , 90%, or 100% identical to one of the sequences exemplified in this disclosure; in order if increasing preference. The length of the identical or homologous sequence compared with the native human polynucleotide can be about 7, 10, 15, 20, 30, 50 or 100 residues in order of increasing preference, up to the length of the entire encoding region.

Polypeptides can be tested for an ability to modulate TRRE in a TNF-R cleavage assay. The polypeptide is contacted with the receptor (preferably expressed on the surface of a cell, such as a C75 cell), and the ability of the polypeptide to increase or decrease receptor cleavage and release is

determined. Cleavage of TNF-R by exemplary polypeptides of this invention is illustrated in Example 7.

Polypeptides of this invention can be used as immunogens for raising antibody. Large proteins will raise a cocktail of antibodies, while short peptide fragments will raise antibodies against small region of the intact protein. Antibody clones can be mapped for protein binding site by producing short overlapping peptides of about 10 amino acids in length. Overlapping peptides can be prepared on a nylon membrane support by standard F-Moc chemistry, using a SPOTS™ kit from Genosys according to manufacturer's directions.

Polypeptides of this invention can also be used to affect TNF signal transduction, as explained below.

Antibodies

Polyclonal antibodies can be prepared by injecting a vertebrate with a polypeptide of this invention in an immunogenic form. Immunogenicity of a polypeptide can be enhanced by linking to a carrier such as KLH, or combining with an adjuvant, such as Freund's adjuvant. Typically, a priming injection is followed by a booster injection is after about 4 weeks, and antiserum is harvested a week later. Unwanted activity cross-reacting with other antigens, if present, can be removed, for example, by running the preparation over adsorbants made of those antigens attached to a solid phase, and collecting the unbound fraction. If desired, the specific antibody activity can be further purified by a combination of techniques, which may include protein, A chromatography, ammonium sulfate precipitation, ion exchange chromatography, HPLC, and immunoaffinity chromatography using the immunizing polypeptide coupled to a solid support. Antibody fragments and other derivatives can be prepared by standard immunochemical methods, such as subjecting the antibody to cleavage with enzymes such as papain or pepsin.

Production of monoclonal antibodies is described in such standard references as Harrow & Lane (1988), U.S. Patent Nos. 4,491,632, 4,472,500 and 4,444,887, and *Methods in Enzymology* 73B:3 (1981). Briefly, a mammal is

immunized, and antibody-producing cells (usually splenocytes) are harvested. Cells are immortalized by fusion with a non-producing myeloma, transfecting with Epstein Barr Virus, or transforming with oncogenic DNA. The treated cells are cloned and cultured, and the clones are selected that produce antibody of the desired specificity.

Other methods of obtaining specific antibody molecules (optimally in the form of single-chain variable regions) involve contacting a library of immunocompetent cells or viral particles with the target antigen, and growing out positively selected clones. Immunocompetent phage can be constructed to express immunoglobulin variable region segments on their surface. See Marks et al., *New Eng. J. Med.* 335:730, 1996, International Patent Applications WO 9413804, WO 9201047, WO 90 02809, and McGuiness et al., *Nature Biotechnol.* 14:1449, 1996.

The antibodies of this invention are can be used in immunoassays for TRRE modulators. General techniques of immunoassay can be found in "The Immunoassay Handbook", Stockton Press NY, 1994; and "Methods of Immunological Analysis", Weinheim: VCH Verlags gesellschaft mbH, 1993). The antibody is combined with a test sample under conditions where the antibody will bind specifically to any modulator that might be present, but not any other proteins liable to be in the sample. The complex formed can be measured in situ (U.S. Patent Nos. 4,208,479 and 4,708,929), or by physically separating it from unreacted reagents (U.S. Patent No. 3,646,346). Separation assays typically involve labeled TRRE reagent (competition assay), or labeled antibody (sandwich assay) to facilitate detection and quantitation of the complex. Suitable labels are radioisotopes such as ^{125}I, enzymes such as β-galactosidase, and fluorescent labels such as fluorescein. Antibodies of this invention can also be used to detect TRRE modulators in fixed tissue sections by immunohistology. The antibody is contacted with the tissue, unreacted antibody is washed away, and then bound antibody is detected — typically using a labeled anti-immunoglobulin reagent. Immunohistology will show not only whether the modulator is present, but where it is located in the tissue.

Detection of TRRE modulators is of interest for research purposes, and for clinical use. As indicated earlier, high expression of TRRE modulators may correlate with progression of cancer. Diagnostic tests are also of use in monitoring TRRE modulators that are administered in the course of therapy.

Antibodies of this invention can also be used for preparation of medicaments. Antibodies with therapeutic potential include those that affect TRRE activity — either by promoting clearance of a TRRE modulator, or by blocking its physiological action. Antibodies can be screened for desirable activity according to assays described in the next section.

Screening assays

This invention provides a number of screening methods for selecting and developing products that modulate TRRE, and thus affect TNF signal transduction.

One screening method is for polynucleotides that have an ability to modulate TRRE activity. To do this screening, cells are obtained that express both TRRE and the TNF receptor. Suitable cell lines can be constructed from any cell that expresses a level of functional TRRE activity. These cells are identifiable by testing culture supernatant for an ability to release membrane-bound TNF-R. The level of TRRE expression should be moderate, so that an increase in activity can be detected. The cells can then be genetically altered to express either p55 or p75 TNF-R, illustrated in Example 1. Exemplary is the C75R line: COS-1 cells genetically altered to express the 75 kDa form of the TNF-R. Release of TNF-R from the cell can be measured either by testing residual binding of labeled TNF ligand to the cell, or by immunoassay of the supernatant for released receptor (Example 1).

The screening assay is conducted by contacting the cells expressing TRRE and TNF-R with the polynucleotides to be screened. The effect of the polynucleotide on the enzymatic release of TNF-R from the cell is determined, and polynucleotides with desirable activity (either promoting or inhibiting TRRE activity) are selected. In a variation of this method, cells expressing TRRE

activity but not TNF-R (such as untransfected COS-1 cells) are contacted with the test polynucleotide. Then the culture medium is collected, and used to assay for TRRE activity using a second cell expressing TNF-R (such as C75 cells).

This type of screening assay is useful for the selection of polynucleotides from an expression library believed to contain encoding sequences for TRRE modulators. The Jurkat cell expression library (ATCC Accession No. TIB-152) is exemplary. Other cells from which suitable libraries can be constructed are those known to express high levels of TRRE, especially after PMA stimulation, such as THP-1, U-937, HL-60, ME-180, MRC-5, Raji, K-562, and normal human monocytes. The screening involves expressing DNA from the library in the selected cell line being used for screening. Wells with the desired activity are selected, and the DNA is recovered, optionally after replication or cloning of the cells. Repeat cycles of functional screening and selection can lead to identification of new polynucleotide clones that promote or inhibit TRRE activity. This is illustrated below in Example 5. Further experiments can be performed on the selected polynucleotides to determine it modulates TRRE activity inside the cell, or through the action of a protein product. A long open reading frame suggests a role for a protein product, and examination of the amino acid sequence for a signal peptide and a membrane spanning region can help determine whether the protein is secreted from the cell or expressed in the surface membrane.

This type of screening is also useful for further development of the polynucleotides of this invention. For example, expression constructs can be developed that encode functional peptide fragments, fusion proteins, and other variants. The minimum size of polynucleotide sequence that still encodes TRRE modulation activity can be determined by removing part of the sequence and then using the screening assay to determine whether the activity is still present. Mutated and extended sequences can be tested in the same way.

This type of screening assay is also useful for developing compounds that affect TRRE activity by interfering with mRNA that encode a TRRE modulator. Of particular interest are ribozymes and antisense oligonucleotides. Ribozymes

are endoribonucleases that catalyze cleavage of RNA at a specific site. They comprise a polynucleotide sequence that is complementary to the cleavage site on the target, and additional sequence that provide the tertiary structure to effect the cleavage. Construction of ribozymes is described in U.S. Patent Nos. 4,987,071 and 5,591,610. Antisense oligonucleotides that bind mRNA comprise a short sequence complementary to the mRNA (typically 8-25 bases in length). Preferred chemistry for constructing antisense oligonucleotides is outlined in an earlier section. Specificity is provided both by the complementary sequence, and by features of the chemical structure. Antisense molecules that inhibit expression of cell surface receptors are described in U.S. Patent Nos. 5,135,917 and 5,789,573. Screening involves contacting the cell expressing TRRE activity and TNF-R with the compound and determining the effect on receptor release. Ribozymes and antisense molecules effective in altering expression of a TRRE promoter would decrease TNF-R release. Ribozymes and antisense molecules effective in altering expression of a TRRE inhibitor would increase TNF-R release.

Another screening method described in this disclosure is for testing the ability of polypeptides to modulate TRRE activity (Example 7). Cells expressing both TNF-R and a moderate level of TRRE activity are contacted with the test polypeptides, and the rate of receptor release is compared with the rate of spontaneous release. An increased rate of release indicates that the polypeptide is a TRRE promoter, while a decreased rate indicates that the polypeptide is a TRRE inhibitor. This assay can be used to test the activity of new polypeptides, and develop variants of polypeptides already known to modulate TRRE. The minimum size of polypeptide sequence that still encodes TRRE modulation activity can be determined by making a smaller fragment of the polypeptide and then using the screening assay to determine whether the activity is still present. Mutated and extended sequences can be tested in the same way.

Another screening method embodied in this invention is a method for screening substances that interfere with the action of a TRRE modulator at the protein level. The method involves incubating cells expressing TNF receptor

(such as C75R cells) with a polypeptide of this invention having TNF promoting activity. There are two options for supplying the TRRE modulator in this assay. In one option, the polypeptide is added to the medium of the cells as a reagent, along with the substance to be tested. In another option, the cells are genetically altered to express the TRRE modulator at a high level, and the assay requires only that the test substance be contacted with the cells. This option allows for high throughput screening of a number of test compounds.

Either way, the rate of receptor release is compared in the presence and absence of the test substance, to identify compounds that enhance or diminish TRRE activity. Parallel experiments should be conducted in which the activity of the substance on receptor shedding is tested in the absence of added polypeptide (using cells that don't express the polypeptide). This will determine whether the activity of the test substance occurs via an effect on the TRRE promoter being added, or through some other mechanism.

This type of screening assay is useful for identifying antibodies that affect the activity of a TRRE modulator. Antibodies are raised against a TRRE modulator as described in the previous section. If the antibody decreases TRRE activity in the screening assay, then it has therapeutic potential to lower TRRE activity in vivo. Screening of monoclonal antibodies using this assay can also help identify binding or catalytic sites in the polypeptide.

This type of screening assay is also useful for high throughput screening of small molecule compounds that have the ability to affect the level of TNF receptors on a cell, by way of its influence on a TRRE modulator. Small molecule compounds that have the desired activity are often preferred for pharmaceutical compositions, because they are often more stable and less expensive to produce.

Medicaments and their use

As described earlier, a utility of certain products embodied in this invention is to affect signal transduction from cytokines (particularly TNF). Products that promote TRRE activity have the effect of decreasing TNF receptors on the

surface of cells, which would decrease signal transduction from TNF. Conversely, products that inhibit TRRE activity prevent cleavage of TNF receptors, increasing signal transduction.

The ability to affect TNF signal transduction is of considerable interest in the management of clinical conditions in which TNF signaling contributes to the pathology of the condition. Such conditions include:

- Heart failure. IL-1ß and TNF are believed to be central mediators for perpetuating the inflammatory process, recruiting and activating inflammatory cells. The inflammation depress cardiac function in congestive heart failure, transplant rejection, myocarditis, sepsis, and burn shock.
- Cachexia. The general weight loss and wasting occurring in the course of chronic diseases, such as cancer. TNF is believed to affect appetite, energy expenditure, and metabolic rate.
- Crohn's disease. The inflammatory process mediated by TNF leads to thickening of the intestinal wall, ensuing from lymphedema and lymphocytic infiltration.
- Endotoxic shock. The shock induced by release of endotoxins from gram-negative bacteria, such as E. coli, involves TNF-mediated inflammation
- Arthritis. TNF promotes expression of nitric oxide synthetase, believed to be involved in disease pathogenesis.

Other conditions of interest are multiple sclerosis, sepsis, inflammation brought on by microbe infection, and diseases that have an autoimmune etiology, such as Type I Diabetes.

Polypeptides of this invention that promote TRRE activity can be administered with the objective of decreasing or normalizing TNF signal transduction. For example, in congestive heart failure or Crohn's disease, the polypeptide is given at regular intervals to lessen the inflammatory sequelae. The treatment is optionally in combination with other agents that affect TNF

signal transduction (such as antibodies to TNF or receptor antagonists) or that lessen the extent of inflammation in other ways.

Polynucleotides of this invention can also be used to promote TRRE activity by gene therapy. The encoding sequence is operably linked to control elements for transcription and translation in human cells. It is then provided in a form that will promote entry and expression of the encoding sequence in cells at the disease site. Forms suitable for local injection include naked DNA, polynucleotides packaged with cationic lipids, and polynucleotides in the form of viral vectors (such as adenovirus and AAV constructs). Methods of gene therapy known to the practitioner skilled in the art will include those outlined in U.S. Patent Nos. 5,399,346, 5,827,703, and 5,866,696.

The ability to affect TNF signal transduction is also of interest where TNF is thought to play a beneficial role in resolving the disease. In particular, TNF plays a beneficial role in the necrotizing of solid tumors. Accordingly, products of this invention can be administered to cancer patients to inhibit TRRE activity, thereby increasing TNF signal transduction and improve the beneficial effect.

Embodiments of the invention that inhibit TRRE activity include antisense polynucleotides. A method of conferring long-standing inhibitory activity is to administer antisense gene therapy. A genetic construct is designed that will express RNA inside the cell which in turn will decrease the transcription of the target gene (U.S. Patent No. 5,759,829). In humans, a more frequent form of antisense therapy is to administer the effector antisense molecule directly, in the form of a short stable polynucleotide fragment that is complementary to a segment of the target mRNA (U.S Patent Nos. 5,135,917 and 5,789,573) — in this case, the transcript that encodes the TRRE modulator. Another embodiment of the invention that inhibits TRRE are ribozymes, constructed as described in an earlier section. The function of ribozymes in inhibiting mRNA translation is described in U.S. Patent Nos. 4,987,071 and 5,591,610.

Once a product of this invention is found to have suitable TRRE modulation activity in the in vitro assays described in this disclosure, it is preferable to also test its effectiveness in an animal model of a TNF mediated

disease process. Example 3 describes an LPS model for sepsis that can be used to test promoters of TRRE activity. Example 4 describes a tumor necrosis model, in which TRRE inhibitors could be tested for an ability to enhance necrotizing activity. Those skilled in the art will know of other animal models suitable for testing effects on TNF signal transduction or inflammation. Other illustrations are the cardiac ischemia reperfusion models of Weyrich et al. (*J. Clin. Invest.* 91:2620, 1993) and Garcia-Criado et al. (*J. Am. Coll. Surg.* 181:327, 1995); the pulmonary ischemia reperfusion model of Steinberg et al. (*J. Heart Lung Transplant.* 13:306, 1994), the lung inflammation model of International Patent Application WO 9635418; the bacterial peritonitis model of Sharar et al. (*J. Immunol.* 151:4982, 1993), the colitis model of Meenan et al. (*Scand. J. Gastroenterol.* 31:786, 1996), and the diabetes model of von Herrath et al. (*J. Clin. Invest.* 98:1324, 1996). Models for septic shock are described in Mack et al. *J. Surg. Res.* 69:399, 1997; and Seljelid et al. *Scand. J. Immunol.* 45:683-7.

For use as an active ingredient in a pharmaceutical preparation, a polypeptide, polynucleotide, or antibody of this invention is generally purified away from other reactive or potentially immunogenic components present in the mixture in which they are prepared. Typically, each active ingredient is provided in at least about 90% homogeneity, and more preferably 95% or 99% homogeneity, as determined by functional assay, chromatography, or SDS polyacrylamide gel electrophoresis. The active ingredient is then compounded into a medicament in accordance with generally accepted procedures for the preparation of pharmaceutical preparations, such as described in *Remington's Pharmaceutical Sciences 18th Edition* (1990), E.W. Martin ed., Mack Publishing Co., PA. Steps in the compounding of the medicament depend in part on the intended use and mode of administration, and may include sterilizing, mixing with appropriate non-toxic and non-interfering excipients and carriers, dividing into dose units, and enclosing in a delivery device. The medicament will typically be packaged with information about its intended use.

Mode of administration will depend on the nature of the condition being treated. For conditions that are expected to require moderate dosing and that are at well perfused sites (such as cardiac failure), systemic administration is acceptable. For example, the medicament may be formulated for intravenous administration, intramuscular injection, or absorption sublingually or intranasally. Where it is possible to administer the active ingredient locally, this is usually preferred. Local administration will both enhance the concentration of the active ingredient at the disease site, and minimize effects on TNF receptors on other tissues not involved in the disease process. Conditions that lend themselves to administration directly at the disease site include cancer and rheumatoid arthritis. Solid tumors can be injected directly when close to the skin, or when they can be reached by an endoscopic procedure. Active ingredients can also be administered to a tumor site during surgical resection, being implanted in a gelatinous matrix or in a suitable membrane such as Gliadel® (Guilford Sciences). Where direct administration is not possible, the administration may be given through an arteriole leading to the disease site. Alternatively, the pharmaceutical composition may be formulated to enhance accumulation of the active ingredient at the disease site. For example, the active ingredient can be encapsulated in a liposome or other matrix structure that displays an antibody or ligand capable of binding a cell surface protein on the target cell. Suitable targeting agents include antibodies against cancer antigens, ligands for tissue-specific receptors (e.g., serotonin for pulmonary targeting). For compositions that decrease TNF signal transduction, an appropriate targeting molecule may be the TNF ligand, since the target tissue may likely display an unusually high density of the TNF receptor.

Effective amounts of the compositions of the present invention are those that alter TRRE activity by at least about 10%, typically by at least about 25%, more preferably by about 50% or 75%. Where near complete ablation of TRRE activity is desirable, preferred compositions decrease TRRE activity by at least 90%. Where increase of TRRE activity is desirable, preferred compositions increase TRRE activity by at least 2-fold. A minimum effective amount of the

active compound will depend on the disease being treated, which of the TRRE modulators is selected for use, and whether the administration will be systemic or local. For systemic administration, an effective amount of activity will generally be an amount of the TRRE modulator that can cause a change in the enzyme activity by 100 to 50,000 Units — typically about 10,000 Units. The mass amount of protein, nucleic acid, or antibody is chosen accordingly, based on the specific activity of the active compound in Units per gram.

The following examples provided as a further guide to the practitioner, and are not intended to limit the invention in any way.

EXAMPLES

Example 1: Assay system for TRRE activity.

This Example illustrates an assay system that measures TRRE activity on the human TNF-R in its native conformation in the cell surface membrane

Membrane-associated TNF-R was chosen as the substrate, as having microenvironment similar to that of the substrate for TRRE in vivo. Membrane-associated TNF-R also requires more specific activity, which would differentiate less-specific proteases. Cells expressing an elevated level of the p75 form of TNF-R were constructed by cDNA transfection into monkey COS-1 cells which express little TNF-R of either the 75 kDa or 55 kDa size.

The procedure for constructing these cells was as follows: cDNA of human p75 TNF-R was cloned from a λgt10 cDNA library derived from human monocytic U-937 cells (Clontech Laboratories, Palo Alto, CA). The first 300 bp on both 5' and 3' ends of the cloned fragment was sequenced and compared to the reported cDNA sequence of human p75 TNF-R. The cloned sequence was a 2.3 kb fragment covering positions 58-2380 of the reported p75 TNF-R sequence, which encompasses the full length of the p75 TNF-R-coding sequence from positions 90-1475. The 2.3 kb p75 TNF-R cDNA was then subcloned into the multiple cloning site of the pCDNA3 eukaryotic expression vector. The

orientation of the p75 TNF-R cDNA was verified by restriction endonuclease mapping.

Figure 1 illustrates the final 7.7 kb construct, pCDTR2. It carries the neomycin-resistance gene for the selection of transfected cells in G418, and the expression of the p75 TNF-R is driven by the cytomegalovirus promoter. The pCDTR2 was then transfected into monkey kidney COS-1 cells (ATCC CRL-1650) using the calcium phosphate-DNA precipitation method. The selected clone in G418 medium was identified and subcultured. This clone was given the designation **C75R.**

To determine the level of p75 TNF-R expression on C75R cells, 2 x 10^5 cells/well were plated into a 24-well culture plate and incubated for 12 to 16 hours in 5% CO_2 at 37°C. They were then incubated with 2-30 ng ^{125}I human recombinant TNF (radiolabeled using the chloramine T method) in the presence or absence of 100-fold excess of unlabeled human TNF at 4°C for 2 h. After three washes with ice-cold PBS, cells were lysed with 0.1N NaOH and bound radioactivity was determined in a Pharmacia Clinigamma counter (Uppsala, Sweden).

Figure 2 shows the results obtained. C75R had a very high level of specific binding of radiolabeled ^{125}I-TNF, while parental COS-1 cells did not. The number of TNF-R expressed on C75R was determined to be 60,000-70,000 receptors per cell by Scatchard analysis (Figure 2, inset). The Kd value calculated was 5.6 x 10^{-10} M. This Kd value was in close agreement to the values previously reported for native p75 TNF-R.

TRRE was obtained by PHA stimulation of THP-1 cells (WO 9802140). THP-1 cells (ATCC 45503) growing in logarithmic phase were collected and resuspended to 1x10^6 cells/ml of RPMI-1640 supplemented with 1% FCS and incubated with 10^{-6} M PMA for 30 min in 5% CO_2 at 37 °C. The cells were collected and washed once with serum-free medium to remove PMA and resuspended in the same volume of RPMI-1640 with 1% FCS. After 2 hours incubation in 5% CO_2 at 37°C, the cell suspension was collected, centrifuged, and the cell-free supernatant was collected as the source of TRRE.

In order to measure the effect of TRRE on membrane-bound TNF-R in the COS-1 cell constructs, the following experiment was performed. C75R cells were seeded at a density of 2 x 10^5 cells/well in a 24-well cell culture plate and incubated for 12 to 16 hours at 37°C in 5% CO_2. The medium in the wells was aspirated, replaced with fresh medium alone or with TRRE medium, and incubated for 30 min at 37°C, The medium was then replaced with fresh medium containing 30 ng/ml ^{125}I-labeled TNF. After 2 hours at 4°C, the cells were lysed with 0.1 N NaOH and the level of bound radioactivity was measured. The level of specific binding of C75R by ^{125}I-TNF was significantly decreased after incubation with TRRE. The radioactive count was 1,393 cpm on the cells incubated with TRRE compared to 10,567 cpm on the cells not treated with TRRE, a loss of 87% of binding capacity.

In order to determine the size of the p75 TNF-R cleared from C75R by TRRE, the following experiment was performed. 15 x 10^6 C75R cells were seeded in a 150 mm cell culture plate and incubated at 37°C in 5% CO_2 for 12 to 16 hours. TRRE medium was incubated with C75R cells in the 150 mm plate for 30 min and the resulting supernatant was collected and centrifuged. The concentrated sample was applied to 10% acrylamide SDS-PAGE and electrophoretically transferred to a polyvinylidene difluoride membrane (Immobilon). Immunostaining resulted in a single band of 40 kDa, similar to the size found in biological fluids. Thus, transfected COS-1 cells expressed high levels of human p75 TNF-R in a form similar to native TNF-R.

The following assay method was adopted for routine measurement of TRRE activity. C75R cells and COS-1 cells were seeded into 24-well culture plates at a density of 2.5 x 10^5 cells/ml/well and incubated overnight (for 12 to 16 hours) in 5% CO_2 at 37°C. After aspirating the medium in the well, 300 µl of TRRE medium was incubated in each well of both the C75R and COS-1 plates for 30 min in 5% CO_2 at 37°C (corresponding to A and C mentioned below, respectively). Simultaneously, C75R cells in 24-well plates were also incubated with 300 µl of fresh medium or buffer . The supernatants were collected,

centrifuged, and then assayed for the concentration of soluble p75 TNF-R by ELISA.

ELISA assay for released TNF-R (WO 9802140) was performed as follows: Polyclonal antibodies to human p75 TNF-R were generated by immunization of New Zealand white female rabbits (Yamamoto et al. *Cell. Immunol.* 38:403-416, 1978). The IgG fraction of the immunized rabbit serum was purified using a protein G (Pharmacia Fine Chemicals, Uppsala, Sweden) affinity column (Ey et al. (1978) *Immunochemistry* 15:429-436, 1978). The IgG fraction was then labeled with horseradish peroxidase (Sigma Chemical Co., St. Louis, MO) (Tijssen and Kurstok, *Anal. Biochem.* 136:451-457, 1984). In the first step of the assay, 5 μg of unlabeled IgG in 100 μl of 0.05 M carbonate buffer (pH 9.6) was bound to a 96-well ELISA microplate (Corning, Corning, NY) by overnight incubation at 4°C. Individual wells were washed three times with 300 μl of 0.2% Tween-20 in phosphate buffered saline (PBS). The 100 μl of samples and recombinant receptor standards were added to each well and incubated at 37°C for 1 to 2 hours. The wells were then washed in the same manner, 100 μl of horseradish peroxidase-labeled IgG added and incubated for 1 hour at 37 °C. The wells were washed once more and the color was developed for 20 minutes (min) at room temperature with the substrates ABTS (Pierce, Rockford, IL) and 30% H_2O_2 (Fisher Scientific, Fair Lawn, NJ). Color development was measured at 405 nm.

When C75R cells were incubated with TRRE medium, soluble p75 TNF-R was released into the supernatant which was measurable by ELISA. The amount of receptors released corresponded to the amount of TRRE added There was also a level of spontaneous TNF-R release in C75R cells incubated with just medium alone. It is hypothesized that this is due to an endogenous source of proteolytic enzyme, a homolog of the human TRRE of monkey origin.

The following calculations were performed. A = (amount of soluble p75 TNF-R in a C75R plate treated with the TRRE containing sample); i.e. the total amount of sTNF-R in a C75R plate. B = (amount of soluble p75 TNF-R spontaneously released in a C75R plate treated with only medium or buffer

containing the same reagent as the corresponding samples but without exogenous TRRE); i.e. the spontaneous release of sTNF-R from C75R cells. C = (amount of soluble p75 TNF-R in a COS-1 plate treated with the TRRE sample or the background level of soluble p75 TNF-R released by THP-1.); i.e. the degraded value of transferred (pre-existing) sTNF-R in the TRRE sample during 30 min incubation in a COS-1 plate. This corresponds to the background level of sTNF-R degraded in a C75R plate. The net release of soluble p75 TNF-R produced only by TRRE activity existing in the initial sample is calculated as follows: (Net release of soluble p75 TNF-R only by TRRE) = A - B - C.

Unit activity of TRRE was defined as follows: 1 pg of soluble p75 TNF-R net release (A-B-C) in the course of the assay is one unit (U) of TRRE activity.

Using this assay, the time course of receptor shedding by TRRE was measured in the following experiment. TRRE-medium was incubated with C75R and COS-1 cells for varying lengths of time. The supernatants were then collected and assayed for the level of soluble p75 TNF-R by ELISA and the net TRRE activity was calculated. Detectable levels of soluble receptor were released by TRRE within 5 min and increased up to 30 min. Longer incubation times showed that the level of TRRE remained relatively constant after 30 min, presumably from the depletion of substrates. Therefore, 30 min was determined to be the optimal incubation time.

The induction patterns of TRRE and known MMPs by PMA stimulation are quite different. In order to induce MMPs, monocytic U-937 cells, fibrosarcoma HT-1080 cells, or peritoneal exudate macrophages (PEM) usually have to be stimulated for one to three days with LPS or PMA. On the other hand, as compared with this prolonged induction, TRRE is released very quickly in culture supernatant following 30 min of PMA-stimulation. The hypothesis that TRRE and sTNF-R form a complex *in vitro* was confirmed by the experiment that 25% TRRE activity was recovered from soluble p75 TNF-R affinity column. This means that free TRRE has the ability to bind to its catalytic product, sTNF-R. The remaining 75% which did not combine to the affinity column may already be

bound to sTNF-R or may not have enough affinity to bind to sTNF-R even though it is in a free form.

Example 2: Characterization of TRRE obtained from THP-1 cells .

TRRE obtained by PHA stimulation of THP-1 cells was partially purified from the culture medium (WO 9802140). First, protein from the medium was concentrated by 100% saturated ammonium sulfate precipitation at 4°C. The precipitate was pelleted by centrifugation at 10,000 x g for 30 min and resuspended in PBS in approximately twice the volume of the pellet. This solution was then dialyzed at 4°C against 10 mM Tris-HCl, 60 mM NaCl, pH 7.0. This sample was loaded on an anion-exchange chromatography, Diethylaminoethyl (DEAE)-Sephadex A-25 column (Pharmacia Biotech) (2.5 x 10 cm) previously equilibrated with 50 mM Tris-HCl, 60 mM NaCl, pH 8.0. TRRE was then eluted with an ionic strength linear gradient of 60 to 250 mM NaCl, 50 mM Tris-HCl, pH 8.0. Each fraction was measured for absorbance at 280 nm and assayed for TRRE activity. The DEAE fraction with the highest specific activity (the highest value of TRRE units/A280) was pooled and used in the characterizations of TRRE described in this example.

In the next experiment, the substrate specificity of the enzyme was elucidated using immunohistochemical techniques. Fluorescein isothiocyanate (FITC)-conjugated anti-CD54, FITC-conjugated goat anti-rabbit and mouse antibodies, mouse monoclonal anti-CD30, anti-CD11b and anti-IL-1R (Serotec, Washington D.C.) were used. Rabbit polyclonal anti-p55 and p75 TNF-R were obtained according to Yamamoto et al. (1978) *Cell Immunol.* 38:403–416. THP-1 cells were treated for 30 min with 1,000 and/or 5,000 U/ml of TRRE eluted from the DEAE-Sephadex column, and then transferred to 12 x 75 mm polystyrene tubes (Fischer Scientific, Pittsburgh, PA) at 1 x 10^5 cells/100µl/tube. The cells were then pelleted by centrifugation at 350 x g for 5 min at 4°C and stained directly with 10µl FITC-conjugated anti-CD54 (diluted in cold PBS/0.5% sodium aside), indirectly with FITC-conjugated anti-mouse antibody after treatment of

mouse monoclonal anti-CD11b, IL-1R and CD30 and also indirectly with FITC-conjugated anti-rabbit antibody after treatment of rabbit polyclonal anti-p55 and p75 TNF-R.

THP-1 cells stained with each of the antibodies without treatment of TRRE were used as negative controls. The tubes were incubated for 45 min at 4°C, agitated every 15 min, washed twice with PBS/2% FCS, repelleted and then resuspended in 200µl of 1% paraformaldehyde. These labeled THP-1 cells were analyzed using a fluorescence activated cell sorter (FACS) (Becton-Dickinson, San Jose, CA) with a 15 mW argon laser with an excitation of 488 nm. Fluorescent signals were gated on the basis of forward and right angle light scattering to eliminate dead cells and aggregates from analysis. Gated signals (10^4) were detected at 585 BP filter and analyzed using Lysis II software. Values were expressed as percentage of positive cells, which was calculated by dividing mean channel fluorescence intensity (MFI) of stained THP-1 cells treated with TRRE by the MFI of the cells without TRRE treatment (negative control cells).

To test the *in vitro* TNF cytolytic assay by TRRE treatment the L929 cytolytic assay was performed according to the method described by Gatanaga et al. (1990b). Briefly, L929 cells, an adherent murine fibroblast cell line, were plated (70,000 cells/0.1ml/well in a 96-well plate) overnight. Monolayered L929 cells were pretreated for 30 min with 100, 500 or 2,500 U/ml of partially-purified TRRE and then exposed to serial dilutions of recombinant human TNF for 1 hour. After washing the plate with RPMI-1640 with 10% FCS to remove the TRRE and TNF, the cells were incubated for 18 hours in RPMI-1640 with 10% FCS containing 1 µg/ml actinomycin D at 37°C in 5% CO_2. Culture supernatants were then aspirated and 50 µl of 1% crystal violet solution was added to each well. The plates were incubated for 15 min at room temperature. After the plates were washed with tap water and air-dried, the cells stained with crystal violet were lysed by 100 µl per well of 100 mM HCl in methanol. The absorbance at

550 nm was measured using an EAR 400 AT plate reader (SLT-Labinstruments, Salzburg, Austria).

To investigate whether TRRE also truncates the ~55 kDa size of TNF-R, partially-purified TRRE was applied to THP-1 cells which express low levels of both p55 and p75 TNF-R (approximately 1,500 receptors/cell by Scatchard analysis). TRRE eluate from the DEAE-Sephadex column was added to THP-1 cells (5 x 10^6 cells/ml) at a final TRRE concentration of 1,000 U/ml for 30 min. The concentration of soluble p55 and p75 TNF-R in that supernatant was measured by soluble p55 and p75 TNF-R ELISA. TRRE was found to truncate both human p55 and p75 TNF-R on THP-1 cells and released 2,382 and 1,662 pg/ml soluble p55 and p75 TNF-R, respectively.

Therefore,TRRE obtained by PHA stimulation of THP-1 cells is capable of enzymatically cleaving and releasing human p75 TNF-R on C75R cells, and both human p55 and p75 TNF-R on THP-1 cells.

Partial inhibition of TRRE activity was obtained by chelating agents such as 1,10-phenanthroline, EDTA and EGTA (% TRRE activity remaining were 41%, 67% and 73%, respectively, at 2 mM concentration). On the other hand, serine protease inhibitors such as PMSF, AEBSF and 3,4-DCI, and serine and cysteine protease inhibitors such as TLCK and TPCK had no effect on the inhibition of TRRE. TRRE was slightly activated in the presence of Mn^{2+}, Ca^{2+}, Mg^{2+}, and Co^{2+} (% TRRE activities remaining were 157%, 151%, 127%, and 123%, respectively), whereas partial inhibition occurred in the presence of Zn^{2+} and Cu^{2+} (% TRRE activities remaining were 23% and 47%, respectively) (WO 9802140).

TRRE fractions from the most active DEAE fraction (60 mM to 250 mM NaCl) can be purified further. In one method (WO 9802140), the fractions were concentrated to 500 µL with a Centriprep-10 filter (10,000 MW cut-off membrane) (Amicon). This concentrated sample was applied to 6% PAGE under non-denaturing native conditions. The gel was sliced horizontally into 5 mm strips and each was eluted into 1 ml PBS. The eluates were then tested according to the assay (Example 1) for TRRE activity.

Example 3: TRRE activity alleviates septic shock

The following protocol was used to test the effects of TRRE in preventing mortality in a model for septic shock. Mice were injected with lethal or sublethal levels of LPS, and then with a control buffer or TRRE. Samples of peripheral blood were then collected at intervals to establish if TRRE blocked TNF-induced production of other cytokines in the bloodstream. Animals were assessed for the ability of TRRE to block the clinical effects of shock, and then euthanized and tissues examined by histopathological methods.

Details were as follows: adult Balb/c mice, were placed in a restraining device and injected intravenously via the tail vein with a 0.1 ml solution containing 10 ng to 10 mg of LPS in phosphate buffer saline (PBS). These levels of LPS induce mild to lethal levels of shock in this strain of mice. Shock results from changes in vascular permeability, fluid loss, and dehydration, and is often accompanied by symptoms including lethargy, a hunched, stationary position, rumpled fur, cessation of eating, cyanosis, and, in serious cases, death within 12 to 24 hours. Control mice received an injection of PBS. Different amounts (2,000 or 4,000 U) of purified human TRRE were injected IV in a 0.1 ml volume within an hour prior to or after LPS injection. Serum (0.1 ml) was collected with a 27 gauge needle and 1 ml syringe IV from the tail vein at 30, 60 and 90 minutes after LPS injection. This serum was heparinized and stored frozen at –20°C. Samples from multiple experiments were tested by ELISA for the presence of sTNF-R, TNF, IL-8 and IL-6. Animals were monitored over the next 12 hours for the clinical effects of shock. Selected animals were euthanized at periods from 3 to 12 hours after treatment, autopsied and various organs and tissues fixed in formalin, imbedded in paraffin, sectioned and stained by hematoxalin-eosin (H and E). Tissue sections were subjected to histopathologic and immunopathologic examination.

Figure 3 shows the results obtained. (◆) LPS alone; (■) LPS plus control buffer; (●) LPS plus TRRE (2,000 U); (▲) LPS plus TRRE (4,000 U).

Mice injected with LPS alone or LPS and a control buffer died shortly after injection. 50% of the test animals were dead after 8 hours (LPS) or 9 hours (LPS plus control buffer), and 100% of the animals were dead at 15 hours. In contrast, animals treated with TRRE obtained as described in Example 1 did much better. When injections of LPS were accompanied by injections of a 2,000 U of TRRE, death was delayed and death rates were lower. Only 40% of the animals were dead at 24 hours. When 4,000 U of TRRE was injected along with LPS, all of the animals had survived at 24 hours. Thus, TRRE is able to counteract the mortality induced by LPS in test animals.

Example 4: TRRE activity decreases tumor necrotizing activity

The following protocol was followed to test the effects of TRRE on tumor necrosis in test animals in which tumors were produced, and in which TNF was subsequently injected.

On Day 0, cutaneous Meth A tumors were produced on the abdominal wall of fifteen BALB/c mice by intradermal injection of 2 x 20^5 Meth A tumor cells. On Day 7, the mice were divided into three groups of five mice each and treated as follows:

- Group 1: Injected intravenously with TNF (1 μg/mouse).
- Group 2: Injected intravenously with TNF (1 μg/mouse) and injected intratumorally with TRRE obtained as in Example 1 (400 units/mouse, 6, 12 hours after TNF injection).
- Group 3: Injected intravenously with TNF (1 μg/mouse) and injected intratumorally with control medium (6, 12 hours after TNF injection).

On Day 8, tumor necrosis was measured with the following results: Group 1: 100% of necrosis (5/5); Group 2: 20% (1/5); Group 3: 80% (4/5). Injections of TRRE greatly reduced the ability of TNF to induce necrosis in Meth A tumors in BALB/c mice.

Since adding TRRE activity ablates the beneficial necrotizing activity of TNF, blocking endogenous TRRE activity would promote the beneficial effects of TNF.

Example 5: Nine new polynucleotide clones that affect TRRE activity

A number of cells have been found to express high levels of TRRE activity, especially after PMA stimulation. These include the cell lines designated THP-1, U-937, HL-60, ME-180, MRC-5, Raji, K-562. Jurkat cells have a high TRRE activity (850 TRRE U/mL at 10^{-2} PMA). In this experiment, the expression library of the Jurkat T cell (ATCC #TIB-152) was obtained and used to obtain 9 polynucleotide clones that augment TRRE activity.

Selection of expression sequences in the library was done by repeated cycles of transfection into COS-1 cells, followed by assaying of the supernatant as in Example 1 for the presence of activity cleaving and releasing the TNF receptor. Standard techniques were used in the genetic manipulation. Briefly, the DNA of 10^6 Jurkat cells was extracted using an InVitrogen plasmid extraction kit according to manufacturer's directions. cDNA was inserted in the ZAP Express™/Eco*RI* vector (cat. no. 938201, Stratagene, La Jolla CA. The library was divided into 48 groups of DNA and transformed into COS-1 cells using the CaCl transfection method. Once the cells were grown out, the TRRE assay was performed, and five positive groups were selected. DNA from each of these five groups was obtained, and transfected into *E. coli*, with 15 plates per group. DNA was prepared from these cells and then transfected into COS-1 cells once more. The cells were grown out, and TRRE activity was tested again. Two positive groups were selected and transfected into *E. coli,* yielding 98 colonies. DNA was prepared from 96 of these colonies and transfected into COS-1 cells. The TRRE activity was performed again, and nine clones were found to substantially increase TRRE activity in the assay. These clones were designated 2-8, 2-9, 2-14, 2-15, P2-2, P2-10, P2-13, P2-14, and P2-15.

Figure 4 is a bar graph showing the TRRE activity observed when the 9 clones were tested with C75 cells in the standard assay (Example 1).

These nine clones were then sequenced according to the following procedure:

1. Plasmid DNA was prepared using a modified alkaline lysis procedure.
2. DNA sequencing was performed using DyeDeoxy termination reactions (ABI). Base-specific fluorescent dyes were used as labels.
3. Sequencing reactions were analyzed on 5.75% Long Ranger™ gels by an ABI 373A-S or on 5.0% Long Ranger™ gels by an ABI 377 automated sequencer.
4. Subsequent data analysis was performed using Sequencher™ 3.0 software.

Standard primers T7X, T3X, -40, -48 Reverse, and BK Reverse (BKR) were used in sequencing reactions. For each clone, several additional internal sequencing primers (listed below) were synthesized.

NCBI BLAST (Basic Local Alignment Search Tool) sequence analysis (Altschul et al. (1990) *J. Mol. Biol.* 215:403-410) was performed to determine if other sequences were significantly similar to these sequences. Both the DNA sequences of the clones and the corresponding ORFs (if any) were compared to sequences available in databases.

The following clones were obtained and sequenced:

TABLE 1: DNA sequences affecting TRRE activity

Clone	Sequence Designation	SEQ ID NO:	Approx. Length (bp)	Expression Designation	Related sequences (potential homology)
2-9	AIM2	1	4,047		—
2-8	AIM3T3 (partial sequence)	2	739		*M. musculus* 45S pre-rRNA gene
	AIM3T7 (partial sequence)	3	233		
2-14	AIM4	4	2,998	Mey3	human arfaptin 2 and others (see below)
2-15	AIM5	5	4,152		—
P2-2	AIM6	6	3,117	Mey5	—
P2-10	AIM7	7	3,306	Mey6	Human Insulin-like Growth factor II Receptor
P1-13	AIM8	8	4,218		—
P2-14	AIM9	9	1,187	Mey8	—
P2-15	AIM10	10	3,306		E1b-55kDa-associated protein

Clone 2-9 (AIM2): The internal primers used for sequencing are shown in SEQ. ID NOS:11-38. The sequence of AIM2 is presented in SEQ ID NO:1. The complementary strand of the AIM2 sequence is SEQ ID NO:147. The longest open reading frame (ORF) in the AIM2 sequence is 474 AA long and represented in SEQ ID NO:148.

Clone 2-8 (AIM3): Two partial sequences of length 739 and 233 were obtained and designated AIM3T3 and AIM3T7. The internal primers used for sequencing are shown in SEQ. ID NOS:39-46. The sequences of AIM3T3 and

AIM3T7 are presented in SEQ ID NOs:2 and 3, respectively. The BLAST search revealed that the AIM3T3 sequence may be homologous to the mouse (*M. musculus*) 28S ribosomal RNA (Hassouna et al. *Nucleic Acids Res.* 12:3563-3583, 1984) and the *M. musculus* 45S pre-rRNA genes (Accession No. X82564. The complementary sequence of the AIM3T3 sequence showed 99% similarity over 408 bp beginning with nt 221 of SEQ ID NO:2 to the former and 97% similarity over the same span to the latter.

Clone 2-14 (AIM4). The internal primers used for sequencing are shown in SEQ. ID NOS:14-65. The sequence of AIM4 is presented in SEQ ID NO:4. The complementary strand of the AIM4 sequence is SEQ ID NO:149. The longest ORF in the AIM4 sequence is 236 AA long and represented in SEQ ID NO:150. AIM4 has significant alignments to human sequences arfaptin 2, ADE2H1 mRNA showing homologies to SAICAR synthetase, polypyrimidine tract binding protein (heterogeneous nuclear ribonucleoprotein I) mRNA, several PTB genes for polypirimidine tract binding proteins, mRNA for por1 protein. Human arfaptin 2 is a putative target protein of ADP-ribosylation factor that interacts with RAC1 by binding directly to it. RAC1 is involved in membrane ruffling. Arfaptin 2 has possible transmembrane segments, potential CK2 phosphorylation sites, PKC phosphorylation site and RGD cell attachment sequence.

Clone 2-15 (AIM5): The internal primers used for sequencing are shown in SEQ. ID NOS:66-80. The sequence of AIM5 is presented in SEQ ID NO:5. The BLAST search revealed that the AIM5 sequence displays some similarity to Human Initiation Factor 5A (eIF-5A) Koettnitz et al. (1995) *Gene* 159:283-284, 1995 and Human Initiation Factor 4D (eIF 4D) Smit-McBride et al. (1989) *J. Biol. Chem.* 264:1578-1583, 1989.

Clone P2-2 (AIM6): The internal primers used for sequencing are shown in SEQ. ID NOS:81-93. The sequence of AIM6 is presented in SEQ ID NO:6. The longest ORF in the AIM6 sequence is 1038 AA long and represented in SEQ ID NO:151.

Clone P2-10 (AIM7): The internal primers used for sequencing are shown in SEQ. ID NOS:94-106. The sequence of AIM7 is presented as SEQ ID NO:7.

The longest ORF in the AIM7 sequence is 849 AA long and represented in SEQ ID NO:152. The BLAST search revealed that this clone may be related to the Human Insulin-like Growth Factor II Receptor (Morgan et al. *Nature* 329:301-307, 1987 or the Human Cation-Independent Mannose 6-Phosphate Receptor mRNA (Oshima et al. *J. Biol. Chem.* 263:2553-2562, 1988). The AIM7 sequence showed roughly 99% identity to both sequences over 2520 nucleotides beginning with nt 12 of SEQ ID NO:7 and 99% similarity to the latter over the same span.

Clone P2-13 (AIM8): The internal primers used for sequencing are shown in SEQ. ID NOS:107-118. The sequence of AIM8 is presented as SEQ ID NO:8. The longest ORF in the AIM8 sequence is 852 AA long and represented in SEQ ID NO:153.

Clone P2-14 (AIM9): The internal primers used for sequencing are shown in SEQ. ID NOS:119-124. The sequence of AIM9 is presented as SEQ ID NO:9. The longest ORF was about 149 amino acids in length.

Clone P2-15 (AIM10): The internal primers used for sequencing are shown in SEQ. ID NOS:125-146. The sequence of AIM10 is presented as SEQ ID NO:10. The longest ORF in the AIM10 sequence is 693 AA long and represented in SEQ ID NO:154. Sequence 10 on BLASTN search of non-redundant databases at NCBI aligns with Human mRNA for E1b-55kDa-associated protein, locus HSA7509 (Accession AJ007509, NID g3319955).

Clonal DNA may be directly injected into test animals in order to test the ability of these nucleic acids to induce TRRE activity, counteract septic shock and/or affect tumor necrosis, as is described in detail in Examples 3 and 4. Alternatively, proteins or RNA can be generated from the clonal DNA for similar testing.

Example 6: Expression of newly obtained clones

Example 5 describes 9 new clones which enhance TRRE activity in a cell surface assay system. The clones were obtained in the pBK-CMB Phagmid vector .

The following work was done on contract through the commercial laboratory Lark Technologies, Houston, TX. The clones were removed from shuttle vectors and inserted into expression vectors in the following manner. Recombinant plasmid (pBK-CMV containing insert) was digested with appropriate restriction enzyme(s) such as Spe I, Xba I, EcoR I or others, as appropriate. The Baculovirus Transfer Vector (pAcGHLT-A Baculovirus Transfer Vector, PharMingen, San Diego, CA, Cat. No. 21460P) was also cut with appropriate restriction enzyme(s) within or near the multiple cloning site to receive the insert removed from the shuttle vector.

The fragment of interest being sublconed was isolated from the digest using Low-Melting agarose electrophoresis and purified from the gel using a Qiaquick Gel Extraction Kit following Lark SOP MB 020602. If necessary, the receiving vector was treated with alkaline phosphatase according to Lark SOP MB 090201. The fragment was ligated into the chosen site of the vector pAcGHLT-A. The recombinant plasmid was transformed into *E. coli* XL1 Blue MRF' cells and the transformed bacterial cells were selected on LB agar plates containing ampicillin (100μg/ml). Ampicillin resistant colonies were picked and grown on LB broth containing ampicillin for plasmid preparation.

Plasmid DNA was prepared using Alkaline Minilysate Procedure (Lark SOP MB 010802 and digested with appropriate restriction enzyme(s). Selected subclones were confirmed to be of the correct size. Sublcones were digested with other appropriate restriction enzyme(s) to ascertain correct orientation of the insert by confirming presence of fragments of proper size(s). A subclone was grown in 100 ml of LB broth containing ampicillin (100μg/ml) and the plasmid DNA prepared using Qiagen Midi Plasmid Preparation Kit (Lark SOP MB 011001). The DNA concentration was determined by measuring the absorbance at 260 nm and the DNA sample was verified to be originated from correct subclone by restriction digestion.

Thus were produced the expression constructs for Mey3, Mey5, Mey6, Mey8 now with the coding sequence of interest fused to GST gene with polyhistitidine tag, protein kinase A site and thrombin cleavage site. The GST

gene and now the fusion protein are under the polyhedrin promotor. PharMingen (San Diego, CA) incorporated the vector with insert into functional baculovirus particles by co-inserting the transfer vector (pAcGHLT) into susceptible insect cell line S along with linearized virus DNA (PharMingen, San Diego, CA, BaculoGold viral DNA, Cat. No. 21100D). The functional virus particles were grown again on the insect cells to generate a high titer stock. Protein production was then done by infecting a large culture of cells in Tini cell. The cells were harvested when the protein yield reached a maximum and before the virus killed the cells. Fusion proteins were collected on a glutatione-agarose column, washed and released with glutathionine.

Proteins collected from the affinity column were quantified by measuring OD_{280} and were assayed on gels using SDS-PAGE and Western blotting with labeled anti-GST (PharMingen, San Diego, CA, mAbGST Cat. No. 21441A) to confirm that all the bands present included the GST portion.

Four of the ten sequences have been cloned, expressed in bacculovirus infected insect cells, and then purified.

TABLE 2: Expressed protein from Jurkat library clones

Name	Sequence in insert	Amount of protein (mg/mL)
Mey3	AIM4	4.7, 5.0
Mey5	AIM6	1.36, 1.50
Mey6	AIM7	0.33
Mey8	AIM9	1.53

Gels indicated the presence of the GST protein in addition to larger proteins that were also positive with the anti-GST antibody in Western analyses. Mey3 repeatedly exhibited the presence of proteins around 32kDa, 56kDa, bands around 60-70kDa and another larger than 70kDa. Mey5 consistently had proteins migrating as approximately 34kDa, 38kDa, 58kDa, around 60-70kDa, and others larger than 70kDa. Mey6 had protein bands around 34kDa, 56kDa,

58kDa, and bands around 60-70kDa. Mey8 had protein bands around 36kDa, 58kDa and bands around 60-70kDa. All of the indicated bands were positive for GST. The bands may represent the desired fusion protein or degradation/cleavage product generated during growth and purification.

Example 7: Assay of expression products for effect on TNF-R cleaving activity

The following method was used to measure TRRE activity of Mey 3, 5, 6 and 8. C75R cells and COS-1 cells were seeded into 24-well culture plates at a density of 2.5 x 10^5 cells/ml/well and incubated overnight (for 12 to16 hours) in 5% CO_2 at 37°C. After aspirating the medium in the well, 300µl of 1 ug of Mey 3, 5 and 8 were incubated in each well of both the C75R and COS-1 plates for 30 min in 5% CO_2 at 37°C (corresponding to A and C mentioned below, respectively). Simultaneously, C75R cells in 24-well plates were also incubated with 300µl of fresh medium or buffer (corresponding to B mentioned below). The supernatants were collected, centrifuged, and then assayed for the concentration of soluble p75 TNF-R by ELISA as described in Example 1.

The following results were obtained:

TABLE 3: Enzymatic activity of expressed clones

Clone No.	TNF-receptor releasing activity U/mg
Mey-3	341
Mey-5	671
Mey-6	452
Mey-8	191

Example 8: Effectiveness of expression products in treating septic shock

The protocol outlined in Example 3 was used to test the effects of the expression products from the new clones in preventing mortality in the septic shock model.

Different amounts of recombinant Mey 3, 5, and 8 (10 – 100 ug/mouse) were injected i.v. in a 0.05 ml volume within an hour prior to or after injection of a lethal dose of LPS. Serum (0.1ml) was collected using a 27 gauge needle and 1 ml syringe from the tail vein at 30, 60 and 90 minutes after LPS injection. This serum was heparinized and stored frozen at -20°C. Samples from multiple experiments were tested by ELISA for the presence of solubilized TNR-R, the TNR ligand, IL-8, and IL-6. Animals were monitored over the next 12 hours for the clinical effects of shock. Selected animals were euthanized from 3 to 12 hours after treatment, autopsied and various organs and tissues fixed in formalin, imbedded in paraffin, sectioned and stained by hematoxalin-eosin (H and E). Tissue sections were subjected to histopathologic and immunopathologic examination.

Figure 5 shows the results obtained. (◆) saline; (■) BSA; (△) Mey-3 (100 μg); (X) Mey-3 (10 μg); (*) Mey-5 (10 μg); (●) Mey-8 (10 μg).

Mice injected with LPS alone or LPS, a control buffer or control protein (BSA) died rapidly. All of the animals in this group were dead at 24 hours. In contrast, when injections of LPS were accompanied by injections of a 10 – 100 ug of Mey 3, 5 and 8, death was delayed and death rates were lower. None of the animal were dead at 24 hours that had been treated with Mey 3 and Mey 5. Only 66 % of the animals were dead at 24 hours that had been treated with Mey 8. Thus, Mey 3, 5 and 8 were able to counteract the mortality induced by LPS in test animals.

ART 34 AMDT

CLAIMS

1. An isolated polynucleotide comprising a nucleotide sequence expressed at the mRNA level in human mononuclear leukocytes having cell-surface TNF receptor, thereby increasing cleavage and release of the receptor from the surface of the cell.

2. The polynucleotide of claim 1, wherein the nucleotide sequence is contained in a sequence selected from the group consisting of
   a) SEQ. ID NO:1;
   b) SEQ. ID NO:2 and SEQ. ID NO:3;
   c) SEQ. ID NO:4;
   d) SEQ. ID NO:5;
   e) SEQ. ID NO:6;
   f) SEQ. ID NO:7;
   g) SEQ. ID NO:8;
   h) SEQ. ID NO:9; and
   i) SEQ. ID NO:10.

3. An isolated polynucleotide comprising at least 30 consecutive nucleotides in said nucleotide sequence of a polynucleotide according to any of claims 1-2.

4. An isolated polynucleotide comprising a linear sequence of at least 50 consecutive nucleotides at least 90% identical to a sequence contained in said nucleotide sequence of the polynucleotide of claim 1.

5. An isolated polynucleotide of at least 50 nucleotides capable of hybridizing specifically to said nucleotide sequence of a polynucleotide according to any of claims 1-3 at 68°C in 0.5 M phosphate buffer pH 7, 7% SDS, and 100 µg/mL salmon sperm DNA, followed by washing in a buffer containing 3X SSC.

6. An antisense polynucleotide or ribozyme comprising at least 10 consecutive nucleotides in said nucleotide sequence of a polynucleotide according to claim 1 or 2, which inhibits the expression of a TRRE modulator.

7. An isolated polypeptide comprising an amino acid sequence encoded by a polynucleotide according to any of claims 1-5.

8. The polypeptide of claim 7, selected from the group consisting of SEQ. ID NOS: 147-154.

9. An isolated polypeptide, comprising at least 10 consecutive residues in said amino acid sequence of a polypeptide according to claim 7 or 8.

10. An isolated polypeptide, comprising at least 15 consecutive amino acids which are at least 80% identical to a sequence contained in said amino acid sequence of the polypeptide according to claim 7 or 8.

11. The polypeptide of claim 7-10, which when incubated with COS-1 cells expressing TNF receptor, promotes enzymatic cleavage and release of the receptor.

12. The polypeptide of claims 7-11, which either:
a) lacks a membrane spanning sequence; or
b) is produced by a process comprising recombinant expression in a host cell followed by purification of the polypeptide from medium in which the cell is cultured.

13. A method of producing the polypeptide according to any of claims 7 to 11, comprising the steps of:
a) culturing host cells genetically altered to express the polynucleotide according to claim 3; and subsequently
b) purifying the polypeptide from the cells.

14. The method according to claim 13, comprising harvesting culture medium following step a); and purifying the polypeptide from the culture medium by a process comprising affinity chromatography.

15. An isolated polynucleotide encoding the polypeptide of claim 8 or 9.

16. An isolated antibody specific for a polypeptide according any of claims 7-11.

17. A method for producing the antibody according to claim 16, comprising immunizing a mammal or contacting an immunocompetent cell or particle with a polypeptide according to claim 9 or 10.

ART 34 AMDT

18. An assay method of determining altered TRRE activity in a cell or tissue sample, comprising the steps of:

a) contacting the sample with the polynucleotide of claim 4 or 5 under conditions that permit the polynucleotide to hybridize specifically with nucleic acid that encodes a modulator of TRRE activity, if present in the sample, and

b) determining polynucleotide that has hybridized as a result of step a), as a measure of altered TRRE activity in the sample.

19. An assay method for determining altered expression of a modulator of TRRE activity in a cell or tissue sample, comprising the steps of:

a) contacting the sample with the antibody of claim 16 under conditions that permit the antibody to bind the modulator if present in the sample, thereby forming an antibody-antigen complex; and

b) determining complex formed in step a), as a measure of the modulator.

20. A method for assessing a disease condition associated with altered TRRE activity in a subject, comprising determining altered TRRE activity in the sample from the subject according to claim 18, or determining altered expression of a TRRE modulator according to claim 19, and then correlating the extent of alteration with the disease condition.

21. A method for decreasing signal transduction from a cytokine into a cell, comprising contacting the cell with a polypeptide according to any of claims 7-8 and 11-12, or with a polynucleotide according to any of claims 1-3 and 15.

22. A method for increasing signal transduction from a cytokine into a cell, comprising contacting the cell with a polynucleotide according to claim 6, or with an antibody according to claim 16.

23. The method according to claim 21 or claim 22, wherein the cytokine is TNF.

24. A method for screening polynucleotides for an ability to modulate TRRE activity, comprising the steps of:

a) providing cells that express both TRRE and the TNF-receptor;

b) genetically altering the cells with the polynucleotides to be screened;

c) cloning the cells genetically altered in step b); and

d) identifying clones that enzymatically release the receptor at an altered rate.

25. A method for screening substances for an ability to affect TRRE activity, comprising the steps of:

a) incubating cells expressing TNF receptor with a polypeptide according to claim 9 in the presence of the substance;

b) incubating cells expressing TNF receptor with a polypeptide according to claim 9 in the absence of the substance;

c) measuring any TNF receptor released from the cells in steps a) and b); and

d) correlating an increase or decrease of the receptor released in step a) relative to that in step b) with an ability of the substance to enhance or diminish TRRE activity.

26. Use of a polypeptide according to any of claims 7-8 or 11-12, in the preparation of a medicament for treatment of the human or animal body by surgery or therapy.

27. Use of a polynucleotide according to any of claims 1-3, 6, or 15 in the preparation of a medicament for treatment of the human or animal body by surgery or therapy.

28. Use of an antibody according to claim 16, in the preparation of a medicament for treatment of the human or animal body by surgery or therapy.

29. Use of a polypeptide according to any of claims 7-8 and 11-12, a polynucleotide according to any of claims 1-3 and 15 or an antibody according to claim 16, in the preparation of a medicament for treatment of a disease selected from the group consisting of heart failure, cachexia, inflammation, endotoxic shock, arthritis, multiple sclerosis, and sepsis.

30. A method of treating cancer in a subject, comprising increasing signal transduction from TNF into cells at the site of the cancer in the subject according to claim 22 or 23.

31. A method of treating a disease selected from the group consisting of heart failure, cachexia, inflammation, endotoxic shock, arthritis, multiple sclerosis, and sepsis, comprising decreasing signal transduction from TNF into cells at the site of the disease in the subject according to claim 21 or 23.

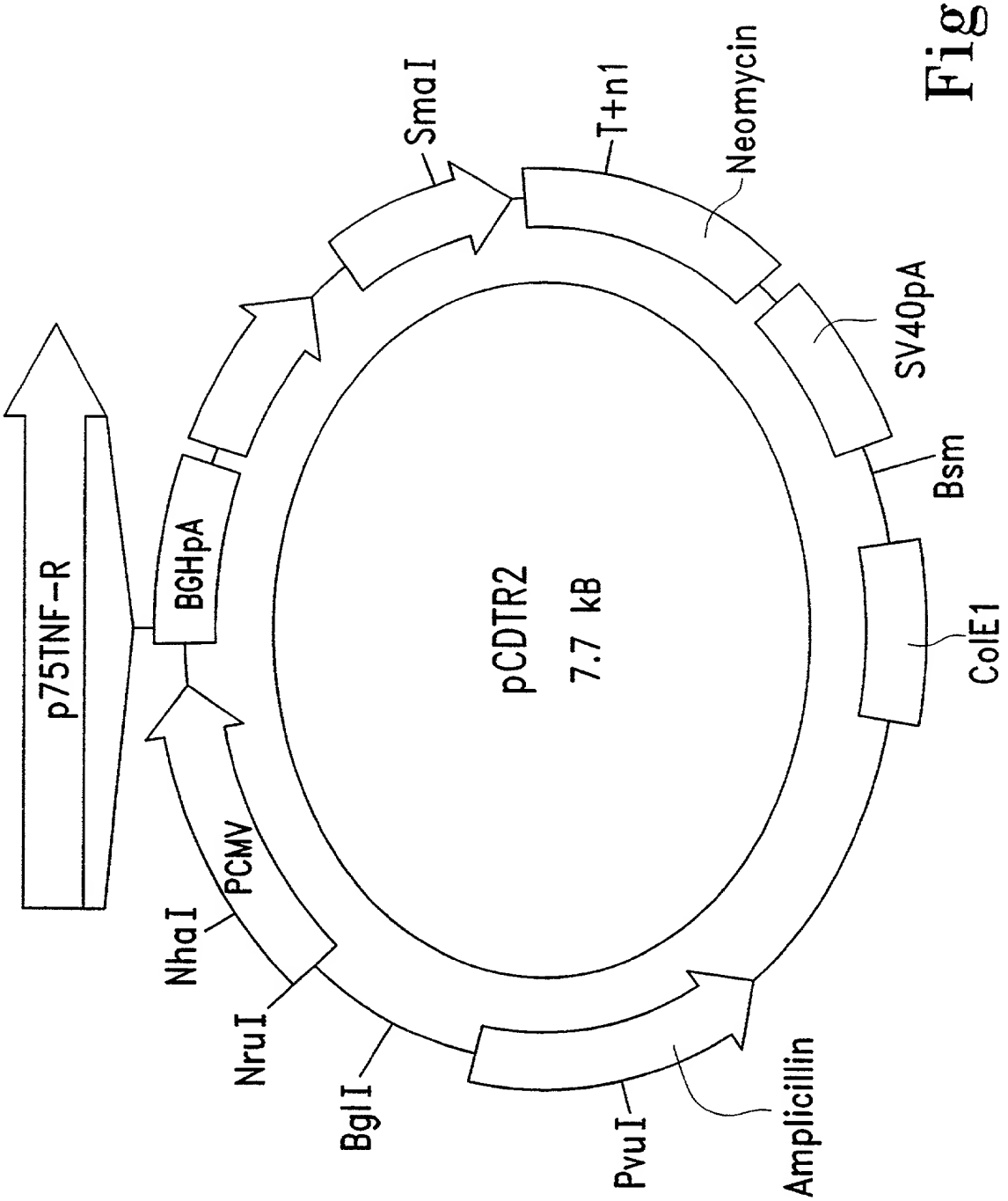
32. The method of claim 31, comprising administering to the subject an effective amount of the polypeptide of any of claims 7-8 or 11-12.

33. The polynucleotide according to any of claims 1-5, wherein said nucleotide sequence is not contained in any of the sequences of the following GenBank Accession Nos: AJ003355, AA806165; AI002979; T33896; U52522; AA779203; C06247; AA707194; AA599596; 5453538; U13369; and J03528.

34. The polypeptide according to any of claims 7-10, the sequence of which is not completely encoded by a polynucleotide sequence contained in any of the sequences of the following GenBank Accession Nos: AJ003355, AA806165; AI002979; T33896; U52522; AA779203; C06247; AA707194; AA599596; 5453538; U13369; and J03528.

35 The polynucleotide according to claim 15, the sequence of which is not contained in any of the sequences of the following GenBank Accession Nos: AJ003355, AA806165; AI002979; T33896; U52522; AA779203; C06247; AA707194; AA599596; 5453538; U13369; and J03528.

36. The isolated polynucleotide of claim 1, wherein the nucleotide sequence is expressed at the mRNA level in Jurkat T cells; and when COS-1 cells expressing TNF receptor are genetically altered to express the sequence, the cells have increased enzymatic activity for cleaving and releasing the receptor.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BGHpA
SmaI
T+n1
Neomycin
SV40pA
Bsm
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pCDTR2
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PCMV
NruI
BglI
PvuI
Amplicillin

Fig. 1

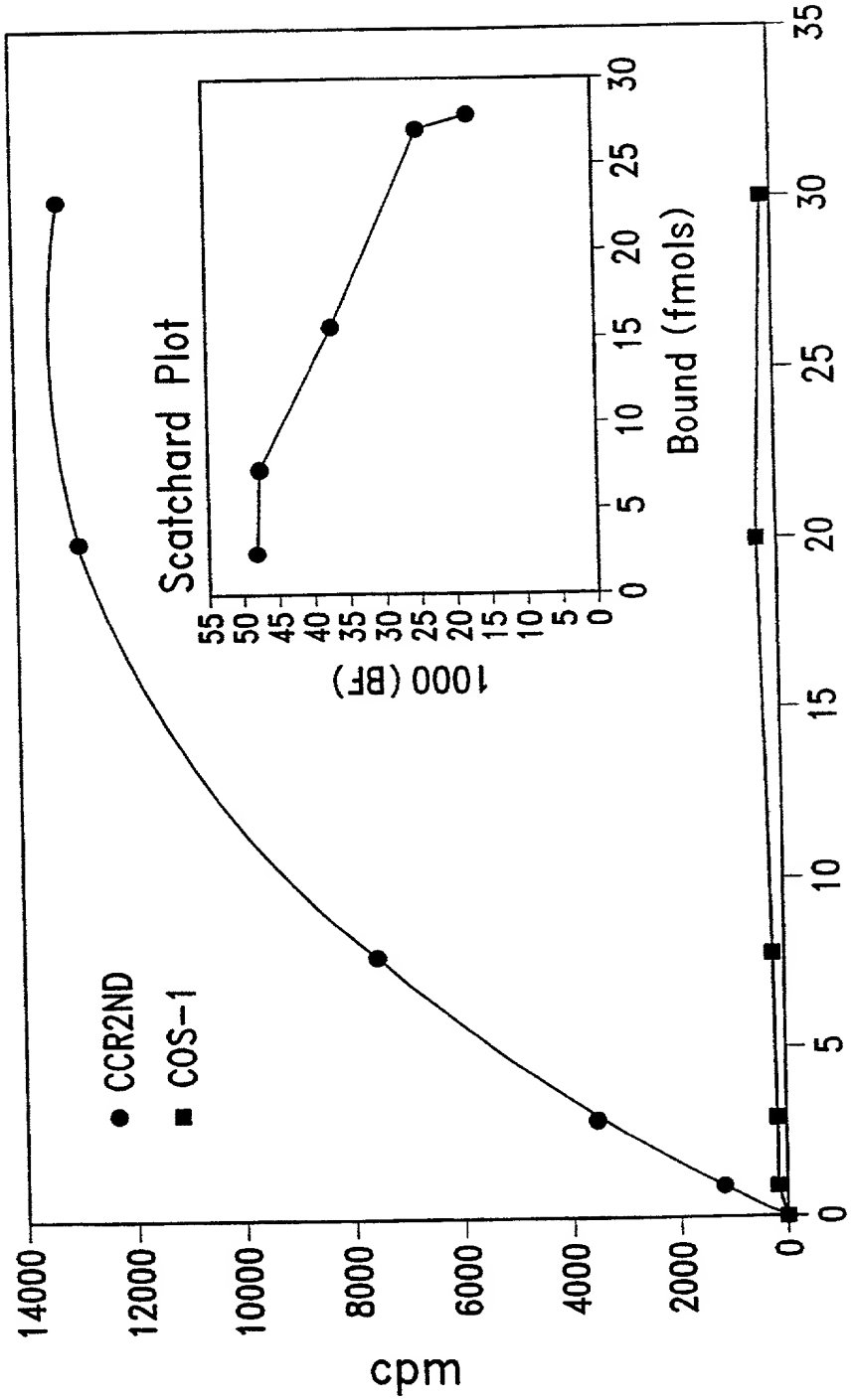

cpm
14000
12000
10000
8000
6000
4000
2000
0
CCR2ND
COS-1
Scatchard Plot
1000 (BF)
55
50
45
40
35
30
25
20
15
10
5
0
Bound (fmols)
35
30
25
20
15
10
5
0
125I-TNF (ng)

Fig. 2

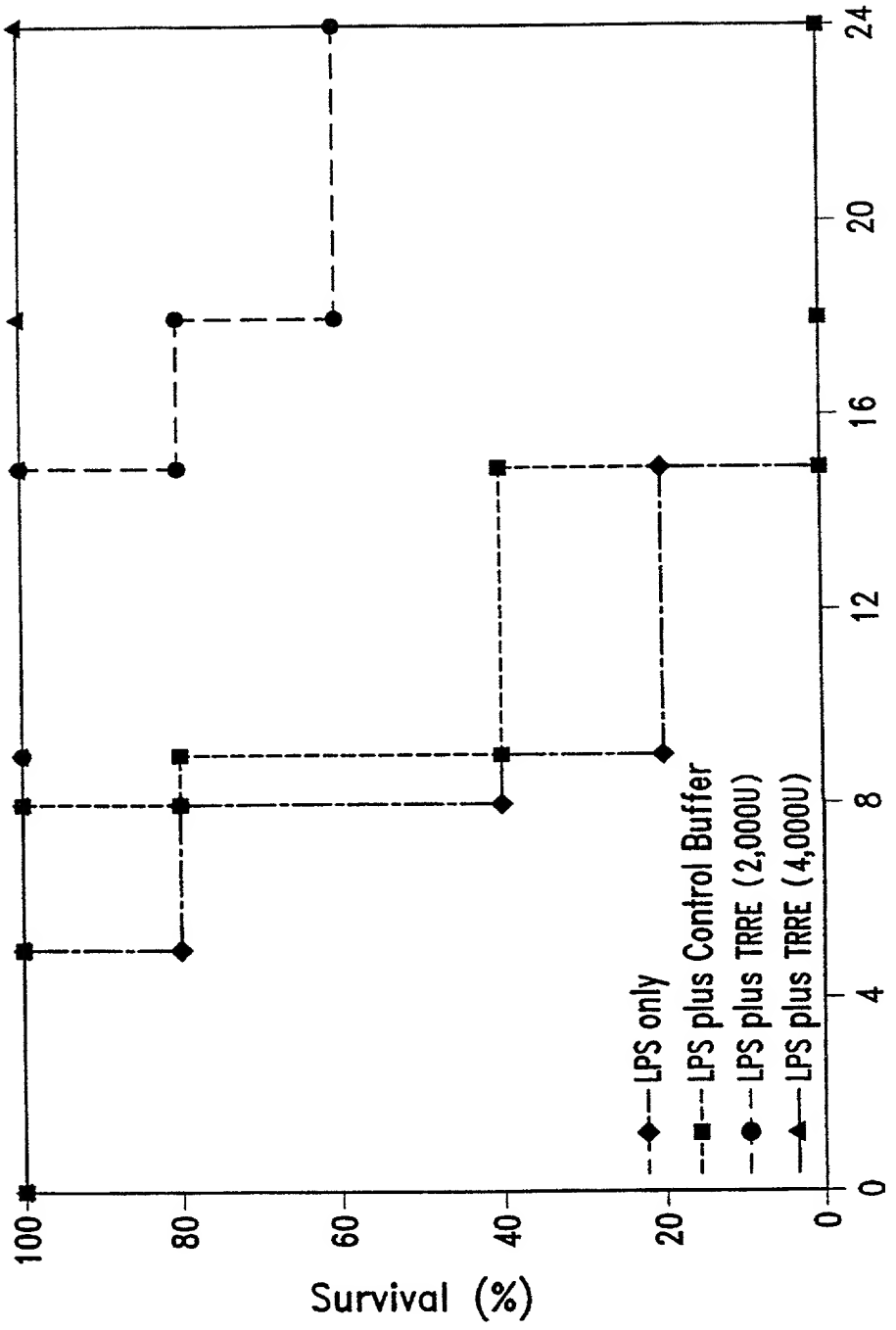
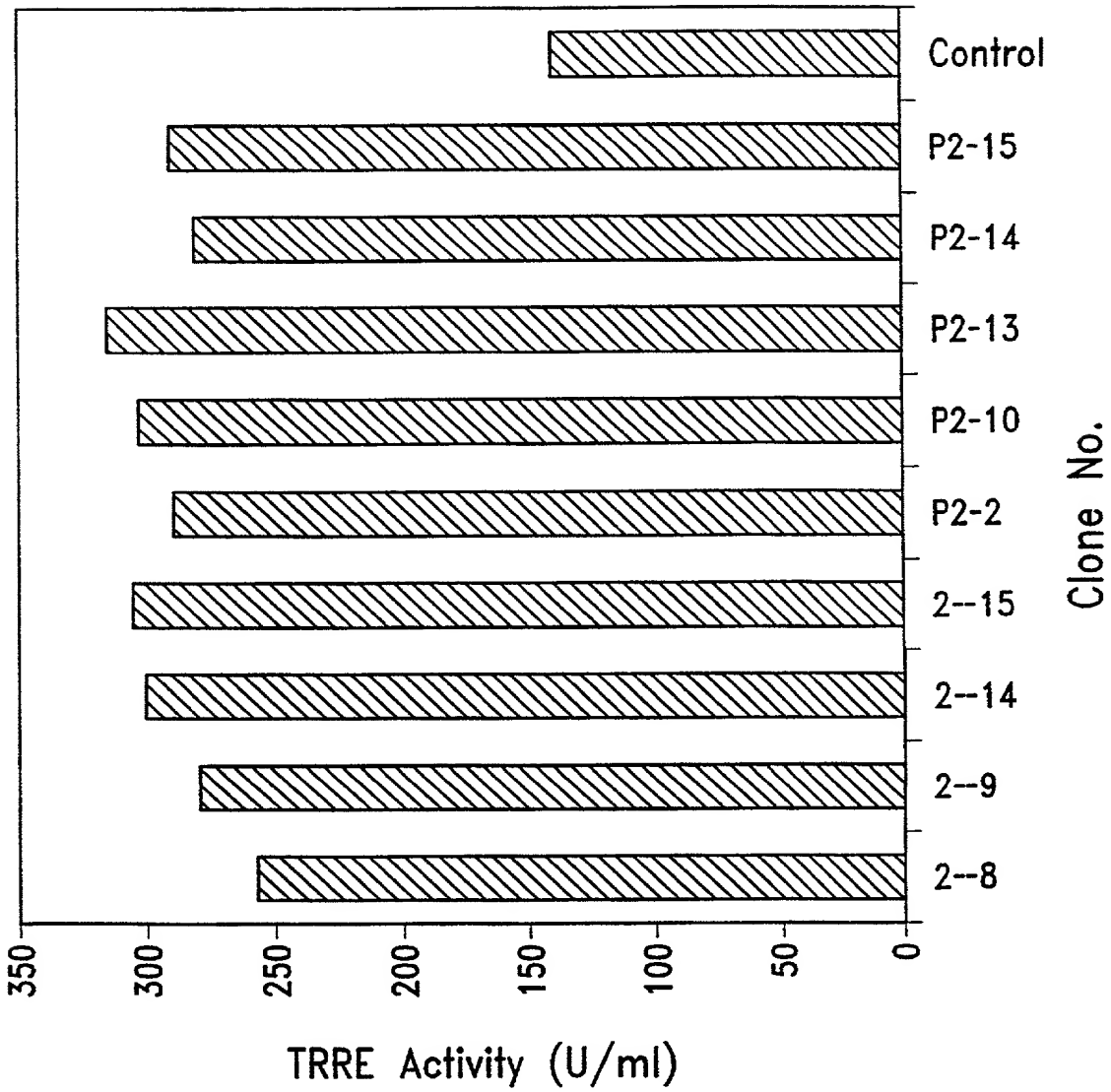

Survival (%)
100
80
60
40
20
0
Time post LPS (hr)
0
4
8
12
16
20
24
LPS only
LPS plus Control Buffer
LPS plus TRRE (2,000U)
LPS plus TRRE (4,000U)

Fig. 3

Fig. 4



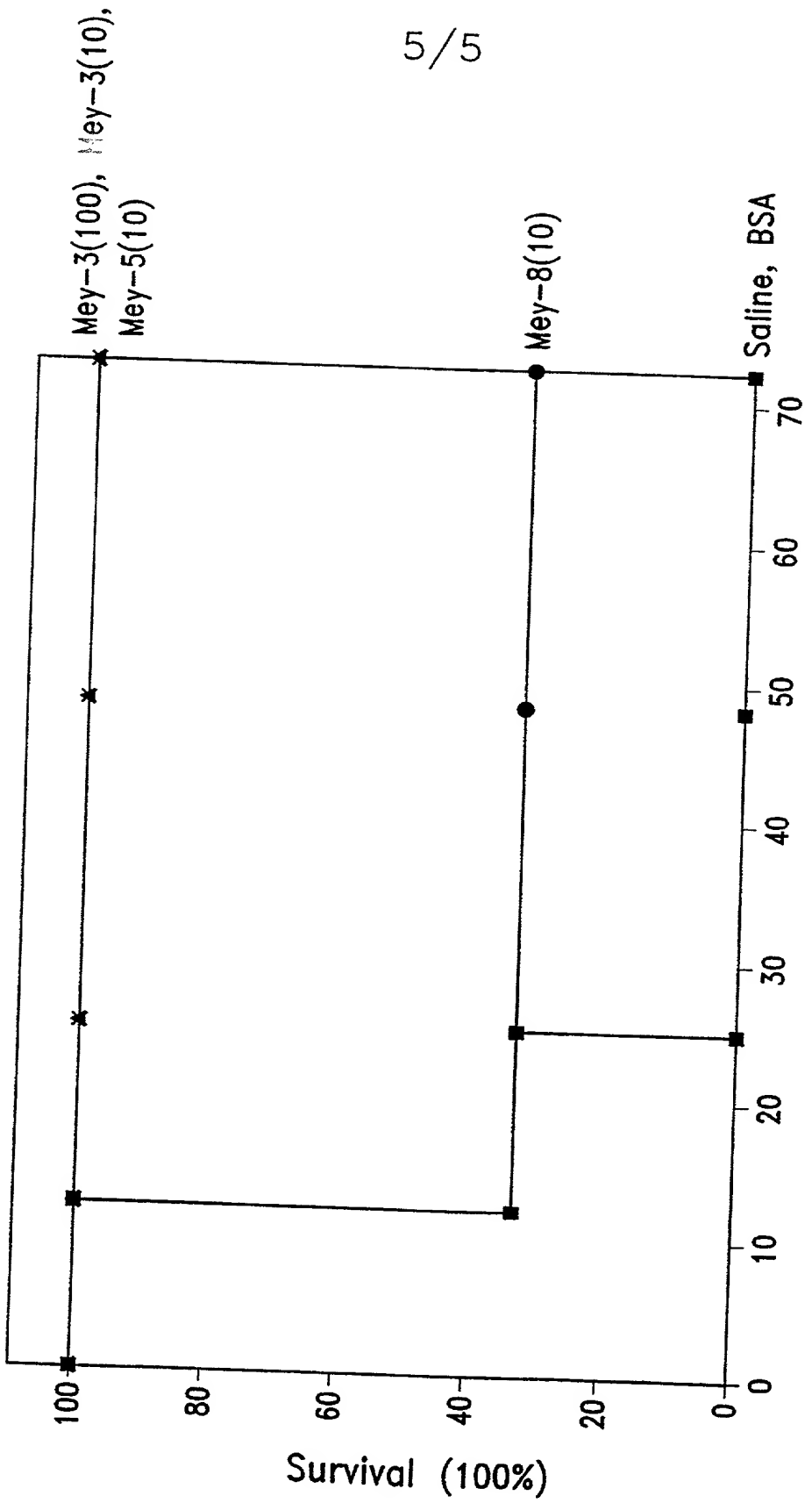

Mey-3(100), Mey-3(10),
Mey-5(10)
Mey-8(10)
Saline, BSA
Survival (100%)
100
80
60
40
20
0
0
10
20
30
40
50
60
70
Time post LPS (hr)

Fig. 5

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER IRVN-007CIP2

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Factors Affecting Tumor Necrosis Factor Receptor Releasing Enzyme Activity ✓
the specification of which (check only one item below):

___ is attached hereto.

___ was filed as United States application

Serial No. _____

on _____,

and was amended

on _____ (if applicable).

X was filed as PCT international application

Number US99/10793 ✓

on May 14, 1999 ✓,

and was amended under PCT Article 19

on January 28, 2000 (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
PCT	PCT/US99/10793	14 May 1999	X YES _ NO
			_ YES _ NO
			_ YES _ NO

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER IRVN-007CIP2

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Factors Affecting Tumor Necrosis Factor Receptor Releasing Enzyme Activity
the specification of which (check only one item below):

___ is attached hereto.

___ was filed as United States application

Serial No. _____

on _____,

and was amended

on _____ (if applicable).

_X_ was filed as PCT international application

Number US99/10793

on May 14, 1999,

and was amended under PCT Article 19

on January 28, 2000 (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
PCT	PCT/US99/10793	14 May 1999	X YES _ NO
			_ YES _ NO
			_ YES _ NO

Combined Declaration For Patent Application and Power of Attorney (Continued) (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER IRVN-007CIP2

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS *(Check one)*		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
09/081,385	May 14, 1998 ✓		XX	

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(List name and registration number)*

Karl Bozicevic, Reg. No. 28,807
Bret E. Field, Reg. No. 37,620
Dianna L. DeVore, Reg. No. 42,484
Alan W. Cannon, Reg. No. 34,977
Carol L. Francis, Reg. No. 36,513
Pamela J. Sherwood, Reg. No. 36,677
Paula A. Borden, Reg. No. 42,344
Nicole Verona, Reg. No. P-47,153

Send Correspondence to:
BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Direct Telephone Calls to:
(name and telephone number)
Name: Carol L. Francis
Registration No. 36,513
Telephone: (650) 327-3400

201	FULL NAME OF INVENTOR	FAMILY NAME Gatanaga	FIRST GIVEN NAME Tetsuya	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY Irvine	STATE OR FOREIGN COUNTRY California CA	COUNTRY OF CITIZENSHIP Japan ✓
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 77 Wellesley	CITY Irvine	STATE & ZIP CODE/COUNTRY California 92612
202	FULL NAME OF INVENTOR	FAMILY NAME Granger	FIRST GIVEN NAME Gale	SECOND GIVEN NAME A.
	RESIDENCE & CITIZENSHIP	CITY Laguna Beach	STATE OR FOREIGN COUNTRY California	COUNTRY OF CITIZENSHIP United States
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 31562 Santa Rosa	CITY Laguna Beach	STATE & ZIP CODE/COUNTRY California

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
DATE 11/13/00	DATE	DATE

M:\FORMS\COMBEC.WP 9/96

Combined Declaration For Patent Application and Power of Attorney (Continued) (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER IRVN-007CIP2

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
09/081,385	May 14, 1998		XX	

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(List name and registration number)*

Karl Bozicevic, Reg. No. 28,807
Bret E. Field, Reg. No. 37,620
Dianna L. DeVoro, Reg. No. 42,484
Alan W. Cannon, Reg. No. 34,977
Carol L. Francis, Reg. No. 36,513
Pamela J. Sherwood, Reg. No. 36,677
Paula A. Borden, Reg. No. 42,344
Nicole Vorona, Reg. No. P-47,153

Send Correspondence to:
BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Direct Telephone Calls to:
(name and telephone number)
Name: Carol L. Francis
Registration No. 36,513
Telephone: (650) 327-3400

201	FULL NAME OF INVENTOR	FAMILY NAME Gatanaga	FIRST GIVEN NAME Tetsuya	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY Irvine	STATE OR FOREIGN COUNTRY California	COUNTRY OF CITIZENSHIP Japan
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 77 Wellesley	CITY Irvine	STATE & ZIP CODE/COUNTRY California 92612
202	FULL NAME OF INVENTOR	FAMILY NAME Granger	FIRST GIVEN NAME Gale	SECOND GIVEN NAME A.
	RESIDENCE & CITIZENSHIP	CITY Laguna Beach	STATE OR FOREIGN COUNTRY California CA	COUNTRY OF CITIZENSHIP United States
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 31562 Santa Rosa	CITY Laguna Beach	STATE & ZIP CODE/COUNTRY California

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
	Gale A Granger	
DATE	DATE 13 NOV 00	DATE

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Gatanaga, Tetsuya
Granger, Gale A.

(ii) TITLE OF INVENTION: Factors Altering Tumor Necrosis Factor Receptor Releasing Enzyme Activity.

(iii) NUMBER OF SEQUENCES: 154

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: BOZICEVIC, FIELD, & FRANCIS, LLP
(B) STREET: 200 MIDDLEFIELD ROAD, #200
(C) CITY: Menlo Park
(D) STATE: CA
(E) COUNTRY: USA
(F) ZIP: 94025

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: Windows
(D) SOFTWARE: FastSEQ for Windows Version 2.0b

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: 09/700,354
(B) FILING DATE: 13-NOV-2000
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 09/081,385
(B) FILING DATE: 14-MAY-1998

(A) APPLICATION NUMBER: PCT/US99/10793
(B) FILING DATE: 14-MAY-1999

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Francis, Carol L.
(B) REGISTRATION NUMBER: 36,513
(C) REFERENCE/DOCKET NUMBER: IRVN-007CIP2

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 650-327-3400
(B) TELEFAX: 650-327-3231
(C) TELEX:

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4047 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 739 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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CGCGCGGCCG GGCGCTTGGC GCCAGAAGCG AGAGCCCCTC GGGGCTCGCC CCCCCGCCTC 120
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CGGACCCCGC CCCGGGCCCC TCGCGGGGAC ACCGGGGGGG CGCCGGGGGC CTCCCACTTA 240
TTCTACACCT CTCATGTCTC TTCACCGTGC CAGACTAGAG TCAAGCTCAA CAGGGTCTTC 300
TTTCCCCGCT GATTCCGCCA AGCCCGTTCC CTTGGCTGTG GTTTCGCTGG ATAGTAGGTA 360
GGGACAGTGG GAATCTCGTT CATCCATTCA TGCGCGTCAC TAATTAGATG ACGAGGCATT 420
TGGCTACCTT AAGAGAGTCA TAGTTACTCC CGCCGTTTAC CCGCGCTTCA TTGAATTTCT 480
TCACTTTGAC ATTCAGAGCA CTGGGCAGAA ATCACATCGC GTCAACACCC GCCGCGGGCC 540
TTCGCGATGC TTTGTTTTAA TTAAACAGTC GGATTCCCCT GGTCCGCACC AGTTCTAAGT 600
CGGCTGCTAG GCGCCGGCCG AAGCGAGGCG CCGCGCGGAA CCGCGGCCCC CGGGGCGGAC 660
CCGCGGGGGG GACCGGGCCG CGGCCCCTCC GCCGCCTGCC GCCGCCGCCG CCGCCGCGCG 720
CCGAAGAAGA AGGGGGAAA 739

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 233 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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CCCCCGCCGC CGCCCCCACG CGGCGCTCCC CCGGGGAGGG GGGAGGACGG GGAGCGGGGG 180
AGAGAGAGAG AGAGAGAGGG CGCGGGGTGG CTCGTGCCGA ATTCAAAAAG CTT 233

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2998 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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GTCCGCCTAC TTTGCTGGGA ACCAGAAACA GCTGGAGCAG ACCCTGCAGC AGTTCAACAT 1500
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CAGCCCAACT TGGCTATCAA GAAAGACATT GGGAAGGGCA GCCCCAGGGT GTGGGAGATT 1620
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CTGCCCTGTC TATCTTCCTG GCCACAGGGC TTCATTCCCA GATCTTTTCC TTCCACTTCA 1800
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CAACTCTACT CTCTCTGCAA CCCACTCAAA GTTTTTCTTT ACCATTTGGA GCCCTTCAGG 2760
AGTTACTTCT TTGAGGTCCC GATAAGACTG TTTGTCTTTC TGTTGGCTTC GATCTCCTGA 2820
TGGCCAGAGT CTCCAGGAAT CATTGTCAAT AACATCAGCA AGAACAATTT CTTTGGTGGT 2880
TACATCAACA CCAAATTCAA TCTTCATATC AACCAGTGTA CAATTCTGGG GCAACCAGGA 2940
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(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4152 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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TGAGCTGCAC GCAGGAACAT GGGCTGCACT CACGACAACA TTGAAAAAAT ATACATTATA 180
TATGTACACC CGGGGCCCCC ACGTCCCCTC CCGTCCCCGC AGCCTGGCCA CACCAGGTCA 240
CGGAGGAGGG GCCGGGGCTG CAGGACCTCA GGACTGCAAG GGCAGGAAGG GAAACAGGAC 300
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GGGAAAAGCT TCCCATGGAC AGGAGAGAGA AGGGAAGGGG AGAGGAGAGG GTTTCCTTCA 480
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CTTTCCAACC CAGCCAGCCC CAGTGCAAGG GGCACACCAG GAGCATGACA GCCCAGAAGT 660
GAGGGATGGG GGGCCGGGGG AGGGGCAGGG CGGACTCCAG AGGGCCCGCT GGGGTTTTGA 720
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AGGTGGGCTT CACCTGAATC TCCACCTCAG CATCATCTGC TGCCCGCTTC TTCCCACAGT 3060
CATAAGCTGT CACTGTAAAC TTATAGAGCC TCTCACCACT GTACTGCAGC TTCTCTGTGT 3120
TCTCAATGTT CCCGTCATTG TCAATGAGGA AAGGGGTGTT GGGTGTGAGA ATCTCATAGT 3180
AGCAGATCTG GCTGTACTGG GGGGAGCAGT CACCGTCAAT GGCTTCCACC CGCAGGATGC 3240
GATCGTACAG CTTCCCCTCT GTCACAGCCG CACGATACAG CCGTTCCACA AACACTGGGG 3300
CAAACTCGTT CACATCGTTG ACCCGCACAT GCACAGTGGC CTTGTGGGAC TTCTTGGTGT 3360
TGGCCCCGTC GGGGCCCTCG CCACAGTCAT AGGCCTGGAT GGTGAAGGTG TGTTCCTTCT 3420
GGGCCTCGCA GTCCACAGGC TCCTTGGCCC GGATCAGCCC CTCTCCTGTC GCCTTGTCAA 3480
GGATCACAGC CTCAAAGGGC ACCCCAGACC CATGGAGCCG GAAGCCGCAG ATCTCACCTG 3540
CATAGCGCAG CGGGGCATCC TTGTCCAAGG CAAAGAGTGG TGGATTCAGT AGGACCGTGT 3600
TGTCATTCTC CATGACGATG CCCTGGTACT CTGCCTCAAT CCATGGCTTG TGCTTGTTGG 3660
CTTTGTTACA GGAGCAGGAC GCGAGCAGAG AGGCCAGCAG AAGGGGCAGC AGCAGGAGGG 3720
TCATGGTGCG GCGTGGGGCA GGGCAGGGCC AGGCGTTTGC CTCCCCTGGG AGCCTCCAGC 3780
CTGCGGATTC CACCTTGCGG GAGGGATACA GGGGGGGAAA ACCAAAATAA AACGTCAAAT 3840
AAATTGTGTA GGAGGAGTCC AGCTTAGGAC CGGGCCAGAG CCAGGCCAGG CTCGGGGAGG 3900
GGGCCTCTGC AGGTTCAGAG GATCACTGCT GCCACCACCG CCACCCTGGG AGCCAGTTAT 3960
TTTGCCATGG CCTTGATTGC AACAGCTGCC TCCTCTGTCA TGGCAGACAG CACCGTGATC 4020
AGGATCTCTT CTCCACAGTC GTACTTCTGC TCAATCTCCT TGCCAAGGTC TCCCTCAGGG 4080
AGACGAAGGT CCTCTCGTAC CTCCCCGCTG TCCTGGAGCA GTGATAGGTA CCCATCCTGG 4140
ATCTTTGGAT CC 4152

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3117 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

GGATCCAAAG ATTCGGCACG AGTGGCCACA TCATGAACCT CCAGGCCCAG CCCAAGGCTC 60
AGAACAAGCG GAAGCGTTGC CTCTTTGGGG GCCAGGAACC AGCTCCCAAG GAGCAGCCCC 120
CTCCCCTGCA GCCCCCCCAG CAGTCCATCA GAGTGAAGGA GGAGCAGTAC CTCGGGCACG 180
AGGGTCCAGG AGGGGCAGTC TCCACCTCTC AGCCTGTGGA ACTGCCCCCT CCTAGCAGCC 240
TGGCCCTGCT GAACTCTGTG GTGTATGGGC CTGAGCGGAC CTCAGCAGCC ATGCTGTCCC 300
AGCAGGTGGC CTCAGTAAAG TGGCCCAACT CTGTGATGGC TCCAGGGCGG GGCCCGGAGC 360
GTGGAGGAGG TGGGGGTGTC AGTGACAGCA GCTGGCAGCA GCAGCCAGGC CAGCCTCCAC 420
CCCATTCAAC ATGGAACTGC CACAGTCTGT CCCTCTACAG TGCAACCAAG GGGAGCCCGC 480

ATCCTGGAGT GGGAGTCCCG ACTTACTATA ACCACCCTGA GGCACTGAAG CGGGAGAAAG 540
CGGGGGGCCC ACAGCTGGAC CGCTATGTGC GACCAATGAT GCCACAGAAG GTGCAGCTGG 600
AGGTAGGGCG GCCCCAGGCA CCCCTGAATT CTTTCCACGC AGCCAAGAAA CCCCCAAACC 660
AGTCACTGCC CCTGCAACCC TTCCAGCTGG CATTCGGCCA CCAGGTGAAC CGGCAGGTCT 720
TCCGGCAGGG CCCACCGCCC CCAAACCCGG TGGCTGCCTT CCCTCCACAG AAGCAGCAGC 780
AGCAGCAGCA ACCACAGCAG CAGCAGCAGC AGCAGCAGGC AGCCCTACCC CAGATGCCGC 840
TCTTTGAGAA CTTCTATTCC ATGCCACAGC AACCCTCGCA GCAACCCCAG GACTTTGGCC 900
TGCAGCCAGC TGGGCCACTG GGACAGTCCC ACCTGGCTCA CCACAGCATG GCACCCTACC 960
CCTTCCCCCC CAACCCAGAT ATGAACCCAG AACTGCGCAA GGCCCTTCTG CAGGACTCAG 1020
CCCCGCAGCC AGCGCTACCT CAGGTCCAGA TCCCCTTCCC CCGCCGCTCC CGCCGCCTCT 1080
CTAAGGAGGG TATCCTGCCT CCCAGCGCCC TGGATGGGGC TGGCACCCAG CCTGGGCAGG 1140
AGGCCACTGG CAACCTGTTC CTACATCACT GGCCCCTGCA GCAGCCGCCA CCTGGCTCCC 1200
TGGGGCAGCC CCATCCTGAA GCTCTGGGAT TCCCGCTGGA GCTGAGGGAG TCGCAGCTAC 1260
TGCCTGATGG GGAGAGACTA GCACCCAATG GCCGGGAGCG AGAGGCTCCT GCCATGGGCA 1320
GCGAGGAGGG CATGAGGGCA GTGAGCACAG GGGACTGTGG GCAGGTGCTA CGGGGCGGAG 1380
TGATCCAGAG CACGCGACGG AGGCGCCGGG CATCCCAGGA GGCCAATTTG CTGACCCTGG 1440
CCCAGAAGGC TGTGGAGCTG GCCTCACTGC AGAATGCAAA GGATGGCAGT GGTTCTGAAG 1500
AGAAGCGGAA AAGTGTATTG GCCTCAACTA CCAAGTGTGG GGTGGAGTTT TCTGAGCCTT 1560
CCTTAGCCAC CAAGCGAGCA CGAGAAGACA GTGGGATGGT ACCCCTCATC ATCCCAGTGT 1620
CTGTGCCTGT GCGAACTGTG GACCCAACTG AGGCAGCCCA GGCTGGAGGT CTTGATGAGG 1680
ACGGGAAGGG TCTTGAACAG AACCCTGCTG AGCACAAGCC ATCAGTCATC GTCACCCGCA 1740
GGCGGTCCAC CCGAATCCCC GGGACAGATG CTCAAGCTCA GGCGGAGGAC ATGAATGTCA 1800
AGTTGGAGGG GGAGCCTTCC GTGCGGAAAC CAAAGCAGCG GCCCAGGCCC GAGCCCCTCA 1860
TCATCCCCAC CAAGGCGGGC ACTTTCATCG CCCCTCCCGT CTACTCCAAC ATCACCCCAT 1920
ACCAGAGCCA CCTGCGCTCT CCCGTGCGCC TAGCTGACCA CCCCTCTGAG CGGAGCTTTG 1980
AGCTACCTCC CTACACGCCG CCCCCCATCC TCAGCCCTGT GCGGGAAGGC TCTGGCCTCT 2040
ACTTCAATGC CATCATATCA ACCAGCACCA TCCCTGCCCC TCCTCCCATC ACGCCTAAGA 2100
GTGCCCATCG CACGCTGCTC CGGACTAACA GTGCTGAAGT AACCCCGCCT GTCCTCTCTG 2160
TGATGGGGGA GGCCACCCCA GTGAGCATCG AGCCACGGAT CAACGTGGGC TCCCGGTTCC 2220
AGGCAGAAAT CCCCTTGATG AGGGACCGTG CCCTGGCAGC TGCAGATCCC CACAAGGCTG 2280
ACTTGGTGTG GCAGCCATGG GAGGACCTAG AGAGCAGCCG GGAGAAGCAG AGGCAAGTGG 2340
AAGACCTGCT GACAGCCGCC TGCTCCAGCA TTTTCCCTGG TGCTGGCACC AACCAGGAGC 2400
TGGCCCTGCA CTGTCTGCAC GAATCCAGAG GAGACATCCT GGAAACGCTG AATAAGCTGC 2460
TGCTGAAGAA GCCCCTGCGG CCCCACAACC ATCCGCTGGC AACTTATCAC TACACAGGCT 2520
CTGACCAGTG GAAGATGGCC GAGAGGAAGC TGTTCAACAA AGGCATTGCC ATCTACAAGA 2580
AGGATTTCTT CCTGGTGCAG AAGCTGATCC AGACCAAGAC CGTGGCCCAG TGCGTGGAGT 2640
TCTACTACAC CTACAAGAAG CAGGTGAAAA TCGGCCGCAA TGGGACTCTA ACCTTTGGGG 2700
ATGTGGATAC GAGCGATGAG AAGTCGGCCC AGGAAGAGGT TGAAGTGGAT ATTAAGACTT 2760
CCCAAAAGTT CCCAAGGGTG CCTCTTCCCA GAAGAGAGTC CCCAAGTGAA GAGAGGCTGG 2820
AGCCCAAGAG GGAGGTGAAG GAGCCCAGGA AGGAGGGGGA GGAGGAGGTG CCAGAGATCC 2880
AAGAGAAGGA GGAGCAGGAA GAGGGGCGAG AGCGCAGCAG GCGGGCAGCG GCAGTCAAAG 2940
CCACGCAGAC ACTACAGGCC AATGAGTCGG CCAGTGACAT CCTCATCCTC CGGAGCCACG 3000
AGTCCAACGC CCCTGGGTCT GCCGGTGGCC AGGCCTCGGA GAAGCCAAGG GAAGGGACAG 3060
GGAAGTCACG AAGGGCACTA CCTTTTTCAG AAAAAAAAAA AAAAAAACAA AAAGCTT 3117

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3306 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GAATTCGGCA CGAGGTCAGT TTCCTGTGGA ACACAGAGGC TGCCTGTCCC ATTCAGACAA 60
CGACGGATAC AGACCAGGCT TGCTCTATAA GGGATCCCAA CAGTGGATTT GTGTTTAATC 120
TTAATCCGCT AAACAGTTCG CAAGGATATA ACGTCTCTGG CATTGGGAAG ATTTTTATGT 180
TTAATGTCTG CGGCACAATG CCTGTCTGTG GGACCATCCT GGGAAAACCT GCTTCTGGCT 240
GTGAGGCAGA AACCCAAACT GAAGAGCTCA AGAATTGGAA GCCAGCAAGG CCAGTCGGAA 300
TTGAGAAAAG CCTCCAGCTG TCCACAGAGG GCTTCATCAC TCTGACCTAC AAAGGGCCTC 360
TCTCTGCCAA AGGTACCGCT GATGCTTTTA TCGTCCGCTT TGTTTGCAAT GATGATGTTT 420
ACTCAGGGCC CCTCAAATTC CTGCATCAAG ATATCGACTC TGGGCAAGGG ATCCGAAACA 480
CTTACTTTGA GTTTGAAACC GCGTTGGCCT GTGTTCCTTC TCCAGTGGAC TGCCAAGTCA 540
CCGACCTGGC TGGAAATGAG TACGACCTGA CTGGCCTAAG CACAGTCAGG AAACCTTGGA 600
CGGCTGTTGA CACCTCTGTC GATGGGAGAA AGAGGACTTT CTATTTGAGC GTTTGCAATC 660
CTCTCCCTTA CATTCCTGGA TGCCAGGGCA GCGCAGTGGG GTCTTGCTTA GTGTCAGAAG 720
GCAATAGCTG GAATCTGGGT GTGGTGCAGA TGAGTCCCCA AGCCGCGGCG AATGGATCTT 780
TGAGCATCAT GTATGTCAAC GGTGACAAGT GTGGGAACCA GCGCTTCTCC ACCAGGATCA 840
CGTTTGAGTG TGCTCAGATA TCGGGCTCAC CAGCATTTCA GCTTCAGGAT GGTTGTGAGT 900
ACGTGTTTAT CTGGAGAACT GTGGAAGCCT GTCCCGTTGT CAGAGTGGAA GGGGACAACT 960
GTGAGGTGAA AGACCCAAGG CATGGCAACT TGTATGACCT GAAGCCCCTG GGCCTCAACG 1020
ACACCATCGT GAGCGCTGGC GAATACACTT ATTACTTCCG GGTCTGTGGG AAGCTTTCCT 1080
CAGACGTCTG CCCCACAAGT GACAAGTCCA AGGTGGTCTC CTCATGTCAG GAAAAGCGGG 1140
AACCGCAGGG ATTTCACAAA GTGGCAGGTC TCCTGACTCA GAAGCTAACT TATGAAAATG 1200
GCTTGTTAAA AATGAACTTC ACGGGGGGGG ACACTTGCCA TAAGGTTTAT CAGCGCTCCA 1260
CAGCCATCTT CTTCTACTGT GACCGCGGCA CCCAGCGGCC AGTATTTCTA AAGGAGACTT 1320
CAGATTGTTC CTACTTGTTT GAGTGGCGAA CGCAGTATGC CTGCCCACCT TTCGATCTGA 1380
CTGAATGTTC ATTCAAAGAT GGGGCTGGCA ACTCCTTCGA CCTCTCGTCC CTGTCAAGGT 1440
ACAGTGACAA CTGGGAAGCC ATCACTGGGA CGGGGGACCC GGAGCACTAC CTCATCAATG 1500
TCTGCAAGTC TCTGGCCCCG CAGGCTGGCA CTGAGCCGTG CCCTCCAGAA GCAGCCGCGT 1560
GTCTGCTGGG TGGCTCCAAG CCCGTGAACC TCGGCAGGGT AAGGGACGGA CCTCAGTGGA 1620
GAGATGGCAT AATTGTCCTG AAATACGTTG ATGGCGACTT ATGTCCAGAT GGGATTCGGA 1680
AAAAGTCAAC CACCATCCGA TTCACCTGCA GCGAGAGCCA AGTGAACTCC AGGCCCATGT 1740
TCATCAGCGC CGTGGAGGAC TGTGAGTACA CCTTTGCCTG GCCCACAGCC ACAGCCTGTC 1800
CCATGAAGAG CAACGAGCAT GATGACTGCC AGGTCACCAA CCCAAGCACA GGACACCTGT 1860
TTGATCTGAG CTCCTTAAGT GGCAGGGCGG GATTCACAGC TGCTTACAGC GAGAAGGGGT 1920
TGGTTTACAT GAGCATCTGT GGGGAGAATG AAAACTGCCC TCCTGGCGTG GGGGCCTGCT 1980
TTGGACAGAC CAGGATTAGC GTGGGCAAGG CCAACAAGAG GCTGAGATAC GTGGACCAGG 2040
TCCTGCAGCT GGTGTACAAG GATGGGTCCC CTTGTCCCTC CAAATCCGGC CTGAGCTATA 2100
AGAGTGTGAT CAGTTTCGTG TGCAGGCCTG AGGCCGGGCC AACCAATAGG CCCATGCTCA 2160
TCTCCCTGGA CAAGCAGACA TGCACTCTCT TCTTCTCCTG GCACACGCCG CTGGCCTGCG 2220
AGCAAGCGAC CGAATGTTCC GTGAGGAATG GAAGCTCTAT TGTTGACTTG TCTCCCCTTA 2280
TTCATCGCAC TGGTGGTTAT GAGGCTTATG ATGAGAGTGA GGATGATGCC TCCGATACCA 2340
ACCCTGATTT CTACATCAAT ATTTGTCAGC CACTAAATCC CATGCACGGA GTGCCCTGTC 2400
CTGCCGGAGC CGCTGTGTGC AAAGTTCCTA TTGATGGTCC CCCCATAGAT ATCGGCCGGG 2460
TAGCAGGACC ACCAATACTC AATCCAATAG CAAATGAGAT TTACTTGAAT TTTGAAAGCA 2520
GTACTCCTTG CCAGGAATTC AGTTGTAAAT AAAATTGAAC CTGCTCAACA GCTGAGGGAG 2580
ACTAGAAATG ATGGGTCCAT ATCCTGGTGC ATTGTCATAC AATTCAAACA ATGGTGCAGC 2640
TACCAGCTTG TAATTTTTAG GGACTGCAAA CAAGGCTTTT TCTTGAAGCT GAACCAGAAA 2700
CAACTTCTTA TGTTCCTTAG GCTTTGTAAT ATGTGCAGGA ATATATGGAT ACTGAGGAGG 2760
TTCAAAATTT GGTCTCCACC AGTTACCAAT GCAATCGTCA ATGACCCAGT CTTGCAAAAC 2820
TCCATCCTGA CGACCCAGTA TCTCTGTCAT TAAGCGTTTT AGTCCTTCAA CTTCATCTTC 2880
TCCTGGGTTA AGTTCACCAC CAGGTAGTTT GAAGAAAGTT GTTCCCAGCT GCAGCAGTAA 2940
CACATGGGGT AGCCGGTGCT CATGTACAAT CAGAACCCCT TCTACAGTCC TCCTCATTCC 3000
AATTTTATCA AATTCTTCCC TCATGCGCTG AAATCTGGCT GCAACAGAGC TGTCCTTCTC 3060
GTAGAGGGGC TCTTTTGTAC CAAAAGTATA ATTGGTAAGA GGGTACAGGT TGATGGTGCG 3120
CTCCAGGGTG AGGGGCTTCG TCTGCTGGAT GTACTTGTTG CCGAACTGAG TGACCCCCCG 3180
GGGCCAGCCG GTCTGCGAGC GATTGGGCGG TACCACAGAC ATGCTGGCGA GCTCCGGCGC 3240
TGACGGCGAG CAGAAAGTGG CAGGCAGGGT AGACTTTCCC CGTGCGGGAA GCCTCGTGCC 3300
GAATTC 3306

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4218 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GAATTCGGCA CGAGAATGGA TCAACCTCAA CAACACGTTA AAGCTAGACG AAAGAAGTAA 60
TACACAGTGT ATGAGTCTCA CATGAAATAC CCGGATGTAA ATCCAAAGAA ACAGGAAGCA 120
GATTGGTGGT TGCCAGGGAC AAGGGCGGTG GGAGGAGAAA ATGGAGAGTA ACGGGACTTT 180
ACTTTTGGAG TGATGAGAAT GTTTTGGAGC TAGATAGAAG TGGTGGTTGT ACACCATTGT 240
GGATGTACTA CCACTTAATT GTTCACTTAA AAAGTTAATT TATGTGAATT GCATCTTAAT 300
TAAAAACAAG GATAACATTC CAACTCCTGG ACATTATCCT TCCTTTCCAT TTGATGTCAG 360
GCCCGTGTTA GAATTCTCAT CCGGTTTGGT CACTGCACTT AAGATGTGGA GAAATTAGGA 420
CGCACAGTTA AGAGGAAGGA TAACACTGAT TAAGGTAGTG CTTTTCTAGG TTTCCCCTAA 480
ACAATTTAAC AGATGGATAG TGGCACCACT TACGAGATGG AAAAACCAGC GGAAGGAAGA 540
TTTGGGGGAG AAGTTAAGTT TGTCTTGGGC CTGTGTTTTG CAACCTGAGT GTAAAAGACA 600
TATGTTAAGT CTTCAGTGGC GAAACACTAA AACTAGAAAT GGATCAGAAT TTTATCTTTG 660
GATGTGACTT CTCAAGGATG GTCTTGTCAC TTCAGTGCCT GGTCAAATGA CAAGATGGGC 720
AATCTTTTCC TGAAGGTCCA AGCACCTGAA CGTGGCAGGG TGACCCGATT CCGATTTGCT 780
TAGAACAATC CTAGTTCATG CCTATTGTCC CTCATGTAAT TAATATCACT CTCAAAATGT 840
CTCATTTTGT GCAATAAATT CTGCAACGTG ATGGCGCGAC TCTCGCGGCC CGAGCGGCCG 900
GACCTTGTCT TCGAGGAAGA GGACCTCCCC TATGAGGAGG AAATCATGCG GAACCAATTC 960
TCTGTCAAAT GCTGGCTTCA CTACATCGAG TTCAAACAGG GCGCCCCGAA GCCCAGGCTC 1020
AATCAGCTAT ACGAGCGGGC ACTCAAGCTG CTGCCCTGCA GCTACAAACT CTGGTACCGA 1080
TACCTGAAGG CGCGTCGGGC ACAGGTGAAG CATCGCTGTG TGACCGACCC TGCCTATGAA 1140
GATGTCAACA ACTGTCATGA GAGGGCCTTT GTGTTCATGC ACAAGATGCC TCGTCTGTGG 1200
CTAGATTACT GCCAGTTCCT CATGGACCAG GGGCGCGTCA CACACACCCG CCGCACCTTC 1260
GACCGTGCCC TCCGGGCACT GCCCATCACG CAGCACTCTC GAATTTGGCC CCTGTATCTG 1320
CGCTTCCTGC GCTCACACCC ACTGCCTGAG ACAGCTGTGC GAGGCTATCG GCGCTTCCTC 1380
AAGCTGAGTC CTGAGAGTGC AGAGGAGTAC ATTGAGTACC TCAAGTCAAG TGACCGGCTG 1440
GATGAGGCCG CCCAGCGCCT GGCCACCGTG GTGAACGACG AGCGTTTCGT GTCTAAGGCC 1500
GGCAAGTCCA ACTACCAGCT GTGGCACGAG CTGTGCGACC TCATCTCCCA GAATCCGGAC 1560
AAGGTACAGT CCCTCAATGT GGACGCCATC ATCCGCGGGG GCCTCACCCG CTTCACCGAC 1620
CAGCTGGGCA AGCTCTGGTG TTCTCTCGCC GACTACTACA TCCGCAGCGG CCATTTCGAG 1680
AAGGCTCGGG ACGTGTACGA GGAGGCCATC CGGACAGTGA TGACCGTGCG GGACTTCACA 1740
CAGGTGTTTG ACAGCTACGC CCAGTTCGAG GAGAGCATGA TCGCTGCAAA GATGGAGACC 1800
GCCTCGGAGC TGGGGCGCGA GGAGGAGGAT GATGTGGACC TGGAGCTGCG CCTGGCCCGC 1860
TTCGAGCAGC TCATCAGCCG GCGGCCCCTG CTCCTCAACA GCGTCTTGCT GCGCCAAAAC 1920
CCACACCACG TGCACGAGTG GCACAAGCGT GTCGCCCTGC ACCAGGGCCG CCCCCGGGAG 1980
ATCATCAACA CCTACACAGA GGCTGTGCAG ACGGTGGACC CCTTCAAGGC CACAGGCAAG 2040
CCCCACACTC TGTGGGTGGC GTTTGCCAAG TTTTATGAGG ACAACGGACA GCTGGACGAT 2100
GCCCGTGTCA TCCTGGAGAA GGCCACCAAG GTGAACTTCA AGCAGGTGGA TGACCTGGCA 2160
AGCGTGTGGT GTCAGTGCGG AGAGCTGGAG CTCCGACACG AGAACTACGA TGAGGCCTTG 2220
CGGCTGCTGC GAAAGGCCAC GGCGCTGCCT GCCCGCCGGG CCGAGTACTT TGATGGTTCA 2280
GAGCCCGTGC AGAACCGCGT GTACAAGTCA CTGAAGGTCT GGTCCATGCT CGCCGACCTG 2340
GAGGAGAGCC TCGGCACCTT CCAGTCCACC AAGGCCGTGT ACGACCGCAT CCTGGACCTG 2400
CGTATCGCAA CACCCCAGAT CGTCATCAAC TATGCCATGT TCCTGGAGGA GCACAAGTAC 2460
TTCGAGGAGA GCTTCAAGGC GTACGAGCGC GGCATCTCGC TGTTCAAGTG GCCCAACGTG 2520
TCCGACATCT GGAGCACCTA CCTGACCAAA TTCATTGCCC GCTATGGGGG CCGCAAGCTG 2580
GAGCGGGCAC GGGACCTGTT TGAACAGGCT CTGGACGGCT GCCCCCCAAA ATATGCCAAG 2640
ACCTTGTACC TGCTGTACGC ACAGCTGGAG GAGGAGTGGG GCCTGGCCCG GCATGCCATG 2700
GCCGTGTACG AGCGTGCCAC CAGGGCCGTG GAGCCCGCCC AGCAGTATGA CATGTTCAAC 2760

ATCTACATCA AGCGGGCGGC CGAGATCTAT GGGGTCACCC ACACCCGCGG CATCTACCAG 2820
AAGGCCATTG AGGTGCTGTC GGACGAGCAC GCGCGTGAGA TGTGCCTGCG GTTTGCAGAC 2880
ATGGAGTGCA AGCTCGGGGA GATTGACCGC GCCCGGGCCA TCTACAGCTT CTGCTCCCAG 2940
ATCTGTGACC CCCGGACGAC CGGCGCGTTC TGGCAGACGT GGAAGGACTT TGAGGTCCGG 3000
CATGGCAATG AGGACACCAT CAAGGAAATG CTGCGTATCC GGCGCAGCGT GCAGGCCACG 3060
TACAACACGC AGGTCAACTT CATGGCCTCG CAGATGCTCA AGGTCTCGGG CAGTGCCACG 3120
GGCACCGTGT CTGACCTGGC CCCTGGGCAG AGTGGCATGG ACGACATGAA GCTGCTGGAA 3180
CAGCGGGCAG AGCAGCTGGC GGCTGAGGCG GAGCGTGACC AGCCCTTGCG CGCCCAGAGC 3240
AAGATCCTGT TCGTGAGGAG TGACGCCTCC CGGGAGGAGC TGGCAGAGCT GGCACAGCAG 3300
GTCAACCCCG AGGAGATCCA GCTGGGCGAG GACGAGGACG AGGACGAGAT GGACCTGGAG 3360
CCCAACGAGG TTCGGCTGGA GCAGCAGAGC GTGCCAGCCG CAGTGTTTGG GAGCCTGAAG 3420
GAAGACTGAC CCGTCCCCTC GTGCCGAATT CGGCACGAGC AAGACCAGCC CCCAGATCAT 3480
TTGCCTCAAA GGTTTTCCCT CGAAGTCACA AATGTTTCAA GGAATCTCAA ATTTTACAAA 3540
GTTTGAAGTG TGGGCATTGG TGGCCTGTGG CTGTGTCCTC TCTCTGTAGC TGTTTTCTCC 3600
CTACATCCCT GAAAGGAAGT TGAGCCTGCT CCTCCATCCG CAGACCTCCC TTTCCAGCGC 3660
CCAGGGCATG GGGTGCTGTG AGGGCAGCAT GCTAGGTGTG ACCGTGCTCC TGGCCTCCAG 3720
GCCCGTGTCC CTCTGTCCTC TAGCCCACTA AGGCCCTGGC CCATTTGTGC TAAACAGGCA 3780
GTCGGACCTA GAAAGAGCAG ACAATCTCTC TGGGTCACCA GTCTGGCTAG GAGCTGGTCT 3840
CCTGACTGGG ATCCAGGCCT TCTCCCCTGC CCATGTGAAT TCCCAGGGGC AGAGCCTGAA 3900
ATGTTGAACA CAGCACTGGC CAAAGAGATG TCACCGTGGG AACCGAGGCT CTCTTCTCCT 3960
CCTGCCTGCT TTCGTGGGTT CAGAGTAGCT GAGGCTTGTC TGAGAGGAGT TGGAGTGCTG 4020
GTTTTCACCC TGGTTGGTGT GCTTTGCTTT GAGGGCACTT AGAAAGCCCA GCCCAGCCCT 4080
TGCTCCTGCC CTGCACACAG CGGAGCGACT TTTCTAGGTA TGCTCTTGAT TTCTGCAGAA 4140
GCAGCAGGTG GCATGGAGCC AAGAGGAAGT GTGACTGAAA CTGTCCACTC ATAGCCCGGC 4200
TGCCGTATTG AGAGGGCT 4218

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1187 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GAGCTCGCGC GCCTGCAGGT CGACACTAGT GGATCCAAAG AATTCGGCAC GAGGGAAACT 60
CAACGGTGTA CGAGTGGAGG ACAGGGACAG AGCCCTCTGT GGTGGAACGA CCCCACCTCG 120
AGGAGCTTCC TGAGCAGGTG GCAGAAGATG CGATTGACTG GGGCGACTTT GGGGTAGAGG 180
CAGTGTCTGA GGGGACTGAC TCTGGCATCT CTGCCGAGGC TGCTGGAATC GACTGGGGCA 240
TCTTCCCGGA ATCAGATTCA AAGGATCCTG GAGGTGATGG GATAGACTGG GGAGACGATG 300
CTGTTGCTTT GCAGATCACA GTGCTGGAAG CAGGAACCCA GGCTCCAGAA GGTGTTGCCA 360
GGGGCCCAGA TGCCCTGACA CTGCTTGAAT ACACTGAGAC CCGGAATCAG TTCCTTGATG 420
AGCTCATGGA GCTTGAGATC TTCTTAGCCC AGAGAGCAGT GGAGTTGAGT GAGGAGGCAG 480
ATGTCCTGTC TGTGAGCCAG TTCCAGCTGG CTCCAGCCAT CCTGCAGGGC CAGACCAAAG 540
AGAAGATGGT TACCATGGTG TCAGTGCTGG AGGATCTGAT TGGCAAGCTT ACCAGTCTTC 600
AGCTGCAACA CCTGTTTATG ATCCTGGCCT CACCAAGGTA TGTGGACCGA GTGACTGAAT 660
TCCTCCAGCA AAAGCTGAAG CAGTCCCAGC TGCTGGCTTT GAAGAAAGAG CTGATGGTGC 720
AGAAGCAGCA GGAGGCACTT GAGGAGCAGG CGGCTCTGGA GCCTAAGCTG GACCTGCTAC 780
TGGAGAAGAC CAAGGAGCTG CAGAAGCTGA TTGAAGCTGA CATCTCCAAG AGGTACAGCG 840
GGCGCCCTGT GAACCTGATG GGAACCTCTC TGTGACACCC TCCGTGTTCT TGCCTGCCCA 900
TCTTCTCCGC TTTTGGGATG AAGATGATAG CCAGGGCTGT TGTTTTGGGG CCCTTCAAGG 960
CAAAAGACCA GGCTGACTGG AAGATGGAAA GCCACAGGAA GGAAGCGGCA CCTGATGGTG 1020
ATCTTGGCAC TCTCCATGTT CTCTACAAGA AGCTGTGGTG ATTGGCCCTG TGGTCTATCA 1080
GGCGAAAACC ACAGATTCTC CTTCTAGTTA GTATAGCGCA AAAAGCTTCT CGAGAGTACT 1140

TCTAGAGCGG CCGCGGGCCC ATCGATTTTC CACCCGGGTG GGGTACC 1187

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3306 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CCCTCACTAA AGGGAACAAA AGCTGGAGCT CGCGCGCCTG CAGGTCGACA CTAGTGGATC 60
GAAAGTTCGT TACGCCAAGC TCGAAATTAA CTCTGGGCTG ACCCATAAAC ATTTGTCTGA 120
TCTAGGATAT AGTTGCGTTT CTTGCGGGCA GCAATCTGGA TGAGGCGGTT GAGGCACTGG 180
GTGGCCTGCT GGATCAGGAC ATCCCAGCGG CCAGCATAGT TCCGCTGCCG GCGTAGGCCC 240
ATCACCCGCA TCTTATCCAT GATGGCATTG GTACCCAGGA TGTTGTACTT CTTGGAAGGG 300
TTGGAGGCTG CATGTTTGAT GGCCCATGTG GTCTTGCCAG CAGCAGGCAG GCCCACCATC 360
ATCAGAATCT CACATTCTGC CTTGCTCTTT GGTCCAACGG TGCCCCGGAT ACGCTCACTA 420
AGGGGAAGGT GCTGGATGAA GGTAAACCCC GGGAGGACAG AACAGTAGGG CTCTGCTCTC 480
TGTCCGAAGT TGAACTCCAC TGCGCAATTC TTCACCAGGA CATGAGGATA GAGGGCCTGA 540
CCCCCCAAGG CTTCCTTCTG GATTCGGAAA GCAATGCCCA TCCACTTTCC ATTCTTGGTA 600
AAAGACAGTT CCACGTCATT TCCACATTCA AAATCCGCAA AGCAGCCAAT CACCGGAGAG 660
CTCTGCGGTG CTAGGAGAGC GGCTGGGCCC GCAGACTGGG GGGAAAGCTC CGCAGCCGCA 720
GTGGGCCCCA GGATCAGGCC CCGCGTGGCC TGGAGAAGCC CAGTCTGGGC TGGAGCGGGA 780
GCTGGACAGT GTGGCCTTGC GTTCGCCCCC GGGAGCGCTG CGAGTGTCGC GGCCTCGGGT 840
GGATTTGCTG AGCACCAATA CCTCACGGTT GCCAACCTGG GGTTTTAGCT CCCTTGGTTT 900
TAATCCCCTA GGGGCGGGTG GGGGCACGGG AGGAAGGATG GGCCAGCTGG GTGCAATCCT 960
GCTGTAAGCC AGCCATTCCT TGATTTCTTA GAATTAACTA AACGGTCGCG CCGGAGGCCG 1020
CGGGGGCCGG AGCGGAGCAG CCGCGGCTGA GGTTCCCGAG TCGGCCGCTC GGGGCTGCGC 1080
TCCGCCGCCG GGACCCCGGC CTCTGGCCGC GCCGGCTCCG GCCTCCGGGG GGGCCGGGGC 1140
CGCCGGGACA TGGTGCCAGT CGCACCCCTT CCCCGCCGCC GCTGAGCTCG CCGGCCGCGC 1200
CCGGGCTGGG ACGTCCGAGC GGGAAGATGT TTTCCGCCCT GAAGAAGCTG GTGGGGTCGG 1260
ACCAGGCCCC GGGCCGGGAC AAGAACATCC CCGCCGGGCT GCAGTCCATG AACCAGGCGT 1320
TGCAGAGGCG CTTCGCCAAG GGGGTGCAGT ACAACATGAA GATAGTGATC CGGGGAGACA 1380
GGAACACGGG CAAGACAGCG CTGTGGCACC GCCTGCAGGG CCGGCCGTTC GTGGAGGAGT 1440
ACATCCCCAC ACAGGAGATC CAGGTCACCA GCATCCACTG GAGCTACAAG ACCACGGATG 1500
ACATCGTGAA GGTTGAAGTC TGGGATGTAG TAGACAAAGG AAAATGCAAA AAGCGAGGCG 1560
ACGGCTTAAA GATGGAGAAC GACCCCCAGG AGNCGGAGTC TGAAATGGCC CTGGATGCTG 1620
AGTTCCTGGA CGTGTACAAG AACTGCAACG GGGTGGTCAT GATGTTCGAC ATTACCAAGC 1680
AGTGGACCTT CAATTACATT CTCCGGGAGC TTCCAAAAGT GCCCACCCAC GTGCCAGTGT 1740
GCGTGCTGGG GAACTACCGG GACATGGGCG AGCACCGAGT CATCCTGCCG GACGACGTGC 1800
GTGACTTCAT CGACAACCTG GACAGACCTC CAGGTTCCTC CTACTTCCGC TATGCTGAGT 1860
CTTCCATGAA GAACAGCTTC GGCCTAAAGT ACCTTCATAA GTTCTTCAAT ATCCCATTTT 1920
TGCAGCTTCA GAGGGAGACG CTGTTGCGGC AGCTGGAGAC GAACCAGCTG GACATGGACG 1980
CCACGCTGGA GGAGCTGTCG GTGCAGCAGG AGACGGAGGA CCAGAACTAC GGCATCTTCC 2040
TGGAGATGAT GGAGGCTCGC AGCCGTGGCC ATGCGTCCCC ACTGGCGGCC AACGGGCAGA 2100
GCCCATCCCC GGGCTCCCAG TCACCAGTCC TGCCTGCACC CGCTGTGTCC ACGGGGAGCT 2160
CCAGCCCCGG CACACCCCAG CCCGCCCCAC AGCTGCCCCT CAATGCTGCC CCACCATCCT 2220
CTGTGCCCCC TGTACCACCC TCAGAGGCCC TGCCCCCACC TGCGTGCCCC TCAGCCCCCG 2280
CCCCACGGCG CAGCATCATC TCTAGGCTGT TTGGGACGTC ACCTGCCACC GAGGCAGCCC 2340
CTCCACCTCC AGAGCCAGTC CCGGCCGCAC AGGGCCCAGC AACGGTCCAG AGTGTGGAGG 2400
ACTTTGTTCC TGACGACCGC CTGGACCGCA GCTTCCTGGA AGACACAACC CCCGCCAGGG 2460
ACGAGAAGAA GGTGGGGGCC AAGGCTGCCC AGCAGGACAG TGACAGTGAT GGGGAGGCCC 2520
TGGGCGGCAA CCCGATGGTG GCAGGGTTCC AGGACGATGT GGACCTCGAA GACCAGCCAC 2580

GTGGGAGTCC CCCGCTGCCT GCAGGCCCCG TCCCCAGTCA AGACATCACT CTTTCGAGTG 2640
AGGAGGAAGC AGAAGTGGCA GCTCCCACAA AAGGCCCTGC CCCAGCTCCC CAGCAGTGCT 2700
CAGAGCCAGA GACCAAGTGG TCCTCCATAC CAGCTTCGAA GCCACGGAGG GGGACAGCTC 2760
CCACGAGGAC CGCAGCACCC CCCTGGCCAG GCGGTGTCTC TGTTCGCACA GGTCCGGAGA 2820
AGCGCAGCAG CACCAGGCCC CCTGCTGAGA TGGAGCCGGG GAAGGGTGAG CAGGCCTCCT 2880
CGTCGGAGAG TGACCCCGAG GGACCCATTG CTGCACAAAT GCTGTCCTTC GTCATGGATG 2940
ACCCCGACTT TGAGAGCGAG GGATCAGACA CACAGCGCAG GGCGGATGAC TTTCCCGTGC 3000
GAGATGACCC CTCCGATGTG ACTGACGAGG ATGAGGGCCC TGCCGAGCCG CCCCCACCCC 3060
CCAAGCTCCC TCTCCCCGCC TTCAGACTGA AGAATGACTC GGACCTCTTC GGGCTGGGGC 3120
TGGAGGAGGC CGGACCCAAG GAGAGCAGTG AGGAAGGTAA GGAGGGCAAA ACCCCCTCTA 3180
AGGAGAAGAA AAAAAAAACA AAAAGCTTCT CGAGAGTACT TCTAGAGCGG CCGCGGGCCC 3240
ATCGATTTTC CACCCGGGTG GGGTACCAGG TAAGTGTACC CAATTCGCCC TATAGTGAGT 3300
CGTATT 3306

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

TGCGGGGCCA GAGTGGGCTG 20

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GCAGTCCTGG CCTGCGGATG 20

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GTCGACAGGA GAATTGGTTC 20

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GCCTGGGTTC GGTGCGGGAC 20

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TGGTCGGGTG TTTGTGAGTG 20

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CCTCTTCCGT CTCCTCAGTG 20

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GGATTGCTAG TCTCACAGAC 20

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

TTAAGGGTGG CTGAAGGGAC 20

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

ACCTTCCCTC CCTGTCACAG 20

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

TGGTCGGGTG TTTGTGAGTG 20

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

ACACCATTCC AGAAATTCAG 20

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

AAACTGCAGG TGGCTGAGTC 20

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GTCCTAATGT TTTCAGGGAG 20

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

AAAACCTATG GTTACAATTC 20

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

TCCTAGACAT GGTTCAAGTG 20

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GATATAATTA GTTCTCCATC 20

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

ATGCCTGTTC CAGGCTGCAC 20

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GGACGGCGAC CTCCACCCAC 20

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GGGCTCCTCC GACGCCTGAG 20

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

AGTCTAGCCC TGGCCTTGAC 20

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GTCACTGGGG ACTCCGGCAG 20

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CAGCTTTCCC TGGGCACATG 20

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CACAGCTGTC TCAAGCCCAG 20

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

ACTGTTCCCC CTACATGATG 20

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

ATCATATCCT CTTGCTGGTC 20

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GTTCCCAGAG CTTGTCTGTG 20

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GTTTGGCAGA CTCATAGTTG 20

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

TAGCAGGGAG CCATGACCTG 20

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CTTGGCGCCA GAAGCGAGAG 20

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

CCTCTCTCTC TCTCTCTCTC 20

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TCCCCGCTGA TTCCGCCAAG 20

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

CTTTTTGAAT TCGGCACGAG 20

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CCCCTGGTCC GCACCAGTTC 20

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GAGAAGGGTC GGGGCGGCAG 20

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

AAATCACATC GCGTCAACAC 20

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

TAAGAGAGTC ATAGTTACTC 20

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

GCTCTAGAAG TACTCTCGAG 20

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

ACTCTGGCCA TCAGGAGATC 20

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CAGGCGTTGT AGATGTTCTG 20

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

AGTGGCAGGC AGAAGTAATG 20

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

GGTTGGAGAA CTGGATGTAG 20

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

CTATTCAGAT GCAACGCCAG 20

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

CCATGGCACA CAGAGCAGAC 20

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

GCTACCATGC AGAGACACAG 20

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

CAGGCTGACA AGAAAATCAG 20

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

GGCACGCATA GAGGAGAGAC 20

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

TGGGTGATGC CTTTGCTGAC 20

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

AAAACAAGAT CAAGGTGATG 20

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

TTGCCCACAT TGCTATGGTG 20

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

GACCAAGATC AGAAGTAGAG 20

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

CCCCTGGGCC AATGATGTTG 20

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

TCTTCCCACC ATAGCAATG 19

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

TGGTCTTGGT GACCAATGTG 20

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

ACACCTCGGT GACCCCTGTG 20

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

TCTCCAAGTT CGGCACAGTG 20

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

ACATGGGCTG CACTCACGAC 20

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

GATCCTCTGA ACCTGCAGAG 20

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

GGAAATGAGG TGGGGCGATC 20

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

CTTTGCCTTG GACAAGGATG 20

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

GCACCTGCCA TTGGGGGTAG 20

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

GGTGGAAGCC ATTGACGGTG 20

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

TGCGTCTCTC GTCGCTGCTG 20

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

GCGGAAACTC TGTGGTGCTG 20

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

AGGATTGCCT TCCTCTACTG 20

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

TGTCTGTTTC ACCAGGGCAG 20

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

CCAGTGCCTC TATGCATGTC 20

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

AGGAAGCCCA CGCACACCAC 20

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

CCCTTTGTTC CCTGATCTTC 20

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

CGCTCGGGAT CCAGGTCATC 20

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

TCGAGGTTCA GAGCGTAGTG 20

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

TCTTGGATCT CTGGCACCTC 20

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

CCATCAGAGT GAAGGAGGAG 20

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

CCATCTTCCA CTGGTCAGAG 20

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

CTCCTTCTCT TGGATCTCTG 20

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

TTACTTCAGC ACTGTTAGTC 20

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

AGGGAGGTAG CTCAAAGCTC 20

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

TGGGTCCACA GTTCGCACAG 20

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

CAACTCTGTG ATGGCTCCAG 20

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

AGCAGGGTTC TGTTCAAGAC 20

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

CCATTGGGTG CTAGTCTCTC 20

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

CAGCCATGCT GTCCCAGCAG 20

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

CTGGACCTGA GGTAGCGCTG 20

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

ATAACCACCC TGAGGCACTG 20

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

CCTGCAGGTC GACACTAGTG 20

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

AATTGGAATG AGGAGGACTG 20

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

GCTCTAGAAG TACTCTCGAG 20

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

ATTGTATGAC AATGCACCAG 20

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

TCCACAGAGG GCTTCATCAC 20

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

CCTGACTGGC CTAAGCACAG 20

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

AAGCCTCATA ACCACCAGTG 20

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

TGTCAACGGT GACAAGTGTG 20

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

TTGTACACCA GCTGCAGGTC 20

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

GGGTGTGGTG CAGATGAGTC 20

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

ATCACACTCT TATAGCTCAG 20

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

GTGGGAAGCT TTCCTCAGAC 20

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

TGATGAACAT GGGCCTGGAG 20

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

CATTGTGGAT GTACTACCAC 20

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

TGTGTTTTGC AACCTGAGTG 20

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

ATAGTGGCAC CACTTACGAG 20

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

AATTCTGCAA CGTGATGGCG 20

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

CACAAGATGC CTCGTCTGTG 20

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

AATCCGGACA AGGTACAGTC 20

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

GCACGAGTGG CACAAGCGTG 20

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

GCAAGCGTGT GGTGTCAGTG 20

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

TGTTTGAACA GGCTCTGGAC 20

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

CGGCATGGCA ATGAGGACAC 20

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

AGGACGAGAT GGACCTCCAG 20

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

CCCTCTGTCC TCTAGCCCAC 20

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

TCTTGAGGGG ACTGACTCTG 20

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

TGAGTGAGGA GGCAGATGTC 20

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

TGGCTTTGAA GAAAGAGCTG 20

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

GCAAAAGACC AGGCTGACTG 20

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

TGCAGCTCCT TGGTCTTCTC 20

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

GATTCACAGT CCCAAGGCTC 20

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

ATCTGGATGA GGCGGTTGAG 20

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

GGTCACTCTC CGACGAGGAG 20

(2) INFORMATION FOR SEQ ID NO:127:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

GGATCCAAAG TTCGTCTCTG 20

(2) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

CGCTGTGTGT CTGATCCCTC 20

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

ATGAAGGTAA ACCCCGGGAG 20

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

TGGTCTCTGG CTCTGAGCAC 20

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

GCCTGGAGAA GCCCAGTCTG 20

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

CACACTCTGG ACCGTTGCTG 20

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

AAAGCTCCGC AGCCGCAGTG 20

(2) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

TCTTCCAGGA AGCTGCGGTC 20

(2) INFORMATION FOR SEQ ID NO:135:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

GATGGTGGGG CAGCATTGAG 20

(2) INFORMATION FOR SEQ ID NO:136:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

GTCACCAGTG GTGCCTGCAG 20

(2) INFORMATION FOR SEQ ID NO:137:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

ACCTCACGGT TGCCAACCTG 20

(2) INFORMATION FOR SEQ ID NO:138:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:

CGCAACAGCG TCTCCCTCTG 20

(2) INFORMATION FOR SEQ ID NO:139:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

AGTACCTTCA TAAGTTCTTC 20

(2) INFORMATION FOR SEQ ID NO:140:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

TCCCAGACTT CAACCTTCAC 20

(2) INFORMATION FOR SEQ ID NO:141:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:

AAACATCTTC CCGGTCGGAC 20

(2) INFORMATION FOR SEQ ID NO:142:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

GCTGAGCACC TTTACCTCAC 20

(2) INFORMATION FOR SEQ ID NO:143:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

GACGTCCGTC CGGGAAGATG 20

(2) INFORMATION FOR SEQ ID NO:144:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:

ACACAGGAGA TGCAGGTCAC 20

(2) INFORMATION FOR SEQ ID NO:145:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

GAGTCTTCCA TGAAGAACAG 20

(2) INFORMATION FOR SEQ ID NO:146:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

GCAGTGAGGA AGGTAAGGAG 20

(2) INFORMATION FOR SEQ ID NO:147:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 4047 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 378...1799
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:

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GGATCCAAAG GACGCCCCCG CCGACAGGAG AATTGGTTCC CGGGCCCGCG GCGATGCCCC     60
CCCGGTAGCT CGGGCCCGTG GTCGGGTGTT TGTGAGTGTT TCTATGTGGG AGAAGGAGGA    120
GGAGGAGGAA GAAGAAGCAA CGATTTGTCT TCTCGGCTGG TCTCCCCCCG GCTCTACATG    180
TTCCCCGCAC TGAGGAGACG GAAGAGGAGC CGTAGCCGCC CCCCCTCCCG GCCCGGATTA    240
TAGTCTCTCG CCACAGCGGC CTCGGCCTCC CCTTGGATTC AGACGCCGAT TCGCCCAGTG    300
TTTGGGAAAT GGGAAGTAAT GACAGCTGGC ACCTGAACTA AGTACTTTTA TAGGCAACAC    360
CATTCCAGAA ATTCAGG ATG AAT GGG GAT ATG CCC CAT GTC CCC ATT ACT        410
                  Met Asn Gly Asp Met Pro His Val Pro Ile Thr
                   1               5                  10

ACT CTT GCG GGG ATT GCT AGT CTC ACA GAC CTC CTG AAC CAG CTG CCT      458
Thr Leu Ala Gly Ile Ala Ser Leu Thr Asp Leu Leu Asn Gln Leu Pro
            15                  20                  25

CTT CCA TCT CCT TTA CCT GCT ACA ACT ACA AAG AGC CTT CTC TTT AAT      506
Leu Pro Ser Pro Leu Pro Ala Thr Thr Thr Lys Ser Leu Leu Phe Asn
        30                  35                  40

GCA CGA ATA GCA GAA GAG GTG AAC TGC CTT TTG GCT TGT AGG GAT GAC      554
Ala Arg Ile Ala Glu Glu Val Asn Cys Leu Leu Ala Cys Arg Asp Asp
    45                  50                  55

AAT TTG GTT TCA CAG CTT GTC CAT AGC CTC AAC CAG GTA TCA ACA GAT      602
Asn Leu Val Ser Gln Leu Val His Ser Leu Asn Gln Val Ser Thr Asp
60                  65                  70                  75

CAC ATA GAG TTG AAA GAT AAC CTT GGC AGT GAT GAC CCA GAA GGT GAC      650
His Ile Glu Leu Lys Asp Asn Leu Gly Ser Asp Asp Pro Glu Gly Asp
                80                  85                  90

ATA CCA GTC TTG TTG CAG GCC GTC CTG GCA AGG AGT CCT AAT GTT TTC      698
Ile Pro Val Leu Leu Gln Ala Val Leu Ala Arg Ser Pro Asn Val Phe
            95                  100                 105

AGG GAG AAA AGC ATG CAG AAC AGA TAT GTA CAA AGT GGA ATG ATG ATG      746
Arg Glu Lys Ser Met Gln Asn Arg Tyr Val Gln Ser Gly Met Met Met
        110                 115                 120

TCT CAG TAT AAA CTT TCT CAG AAT TCC ATG CAC AGT AGT CCT GCA TCT      794
Ser Gln Tyr Lys Leu Ser Gln Asn Ser Met His Ser Ser Pro Ala Ser
    125                 130                 135

TCC AAT TAT CAA CAA ACC ACT ATC TCA CAT AGC CCC TCC AGC CGG TTT      842
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Ser Asn Tyr Gln Gln Thr Thr Ile Ser His Ser Pro Ser Ser Arg Phe
140                 145                 150                 155

GTG CCA CCA CAG ACA AGC TCT GGG AAC AGA TTT ATG CCA CAG CAA AAT      890
Val Pro Pro Gln Thr Ser Ser Gly Asn Arg Phe Met Pro Gln Gln Asn
                160                 165                 170

AGC CCA GTG CCT AGT CCA TAC GCC CCA CAA AGC CCT GCA GGA TAC ATG      938
Ser Pro Val Pro Ser Pro Tyr Ala Pro Gln Ser Pro Ala Gly Tyr Met
            175                 180                 185

CCA TAT TCC CAT CCT TCA AGT TAC ACA ACA CAT CCA CAG ATG CAA CAA      986
Pro Tyr Ser His Pro Ser Ser Tyr Thr Thr His Pro Gln Met Gln Gln
        190                 195                 200

GCA TCG GTA TCA AGT CCC ATT GTT GCA GGT GGT TTG AGA AAC ATA CAT     1034
Ala Ser Val Ser Ser Pro Ile Val Ala Gly Gly Leu Arg Asn Ile His
    205                 210                 215

GAT AAT AAA GTT TCT GGT CCG TTG TCT GGC AAT TCA GCT AAT CAT CAT     1082
Asp Asn Lys Val Ser Gly Pro Leu Ser Gly Asn Ser Ala Asn His His
220                 225                 230                 235

GCT GAT AAT CCT AGA CAT GGT TCA AGT GAG GAC TAC CTA CAC ATG GTG     1130
Ala Asp Asn Pro Arg His Gly Ser Ser Glu Asp Tyr Leu His Met Val
                240                 245                 250

CAC AGG CTA AGT AGT GAC GAT GGA GAT TCT TCA ACA ATG AGG AAT GCT     1178
His Arg Leu Ser Ser Asp Asp Gly Asp Ser Ser Thr Met Arg Asn Ala
            255                 260                 265

GCA TCT TTT CCC TTG AGA TCT CCA CAG CCA GTA TGC TCC CCT GCT GGA     1226
Ala Ser Phe Pro Leu Arg Ser Pro Gln Pro Val Cys Ser Pro Ala Gly
        270                 275                 280

AGT GAA GGA ACT CCT AAA GGC TCA AGA CCA CCT TTA ATC CTA CAA TCT     1274
Ser Glu Gly Thr Pro Lys Gly Ser Arg Pro Pro Leu Ile Leu Gln Ser
    285                 290                 295

CAG TCT CTA CCT TGT TCA TCA CCT CGA GAT GTT CCA CCA GAT ATC TTG     1322
Gln Ser Leu Pro Cys Ser Ser Pro Arg Asp Val Pro Pro Asp Ile Leu
300                 305                 310                 315

CTA GAT TCT CCA GAA AGA AAA CAA AAG AAG CAG AAG AAA ATG AAA TTA     1370
Leu Asp Ser Pro Glu Arg Lys Gln Lys Lys Gln Lys Lys Met Lys Leu
                320                 325                 330

GGC AAG GAT GAA AAA GAG CAG AGT GAG AAA GCG GCA ATG TAT GAT ATA     1418
Gly Lys Asp Glu Lys Glu Gln Ser Glu Lys Ala Ala Met Tyr Asp Ile
            335                 340                 345

ATT AGT TCT CCA TCC AAG GAC TCT ACT AAA CTT ACA TTA AGA CTT TCT     1466
Ile Ser Ser Pro Ser Lys Asp Ser Thr Lys Leu Thr Leu Arg Leu Ser
        350                 355                 360

CGT GTA AGG TCT TCA GAC ATG GAC CAG CAA GAG GAT ATG ATT TCT GGT     1514
Arg Val Arg Ser Ser Asp Met Asp Gln Gln Glu Asp Met Ile Ser Gly
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    365                 370                 375

GTG GAA AAT AGC AAT GTT TCA GAA AAT GAT ATT CCT TTT AAT GTG CAG    1562
Val Glu Asn Ser Asn Val Ser Glu Asn Asp Ile Pro Phe Asn Val Gln
380                 385                 390                 395

TAC CCA GGA CAG ACT TCA AAA ACA CCC ATT ACT CCA CAA GAT ATA AAC    1610
Tyr Pro Gly Gln Thr Ser Lys Thr Pro Ile Thr Pro Gln Asp Ile Asn
                400                 405                 410

CGC CCA CTA AAT GCT GCT CAA TGT TTG TCG CAG CAA GAA CAA ACA GCA    1658
Arg Pro Leu Asn Ala Ala Gln Cys Leu Ser Gln Gln Glu Gln Thr Ala
            415                 420                 425

TTC CTT CCA GCA AAT CAA GTG CCT GTT TTA CAA CAG AAC ACT TCA GTT    1706
Phe Leu Pro Ala Asn Gln Val Pro Val Leu Gln Gln Asn Thr Ser Val
        430                 435                 440

GCT GCA AAA CAA CCC CAG ACC AAT AGT CAC AAA ACC TTG GTG CAG CCT    1754
Ala Ala Lys Gln Pro Gln Thr Asn Ser His Lys Thr Leu Val Gln Pro
    445                 450                 455

GGA ACA GGC ATA GAG GTC TCA GCA GAG CTG CCC AAG GAC AAG ACC TAAGA  1804
Gly Thr Gly Ile Glu Val Ser Ala Glu Leu Pro Lys Asp Lys Thr
460                 465                 470

TCCAGCAGGG AACTATGTAG TCACCCCGAG AGGCCCAGCT CTCTCCGTGA GCTCTGGGCC   1864
TAGGGTGGGG GTGGTTGTTG GTTCTGCGCG CACTGTTCCC CCTACATGAT GGGTCCATCC   1924
CAGTTGGCTT CTCTCACTCG CTTCCTCCTG TGGAGAAGCC TGTCCAGGTG TCACTGCCTC   1984
CAGGAAGCTG TCTCTGATTT CTCCAGTTGA ACAGTGAGAT TTGCCACACC TCACATGCAT   2044
CGCTCTTGTC CCTGGAATTG TAACCATAGG TTTTCCTGTC TCCTGGAGGA CAAGGATGAG   2104
GGCTTTCCAC TTGAGTCTCC CTGGTGGAGC CCAGCTCCTG ACATACCTGG TAAAAGTTCT   2164
CAAGAGAAGA ACATGGAGGA GGAATGTGGA TAACAACCCT GGCTGCCTGT GTGTTCCAAG   2224
CTAGGAAGAT GTAATGTCCC CACAAACGGG GTAAATGGCT TGCCTGCGTC ACAGCTGTCT   2284
CAAGCCCAGG CCCTGGGCGC CAGCCCAAGC CCAAGGACTA GGTCCAGAGC CACACAGCGC   2344
CAGGCCACAT CCGCCTCACC TGGGACCCTT TGTGGGGTAC AGTCTCCGGC CCCACCCAGA   2404
CCTCCTGAAG GAGAGACCCC ATGGCAAGGA CTCAGCCACC TGCAGTTTCA TAAGCCCCCA   2464
GTGGGTTCCT AGGCATGAAG ACCACCGGTT AGAGGCTGAA CTGGCAGGAA CCTGTCTCCA   2524
GCCCCTTCTC ACCCCAGCCG GGCCCTGCCT CAGAGGCAGC ACCCAGGACG TGGCCATGAC   2584
CCGTGGACTC CACTCAATCC CTCTTCTCCA GGAGCCATGC AAAGTGTCAG CCAGCCAGGC   2644
CCCTGGAAGG CAGTCATCAC CTCTTAAGGC ATTGTGGGTG TCGGTCCTGC AACTGCCAGG   2704
TGCAGCACAC GACCCGTGTC CGGTGTTCGA TAGCAGGGAG CCATGACCTG GCAACGATTC   2764
CACGCTCAAA GGGGCACCCG GGGGGCCCTG GGTCGGGGCG GATCAGCTTT CCCTGGGCAC   2824
ATCTGCCTCA TTCCAGATCT CCAGGGCTCA TGTCTGTGAC AGGGAGGGAA GGCTCTGCCC   2884
TGGCCTTCCG TCAGCTCTGC CAGTGCAGGC TGGGCAGCCT GGGCTTTAGA GCTGGCTTCT   2944
GCCCACACTT TCTCCGTGAA AGGAAAACAA CTATGAGTCT GCCAAACGCA TCTCAGATGC   3004
GTTTTAAAAA ATTCTGGTCC CCGCTCTCTG TCCCATCATC CGCCTCGGGG ACTTCCTCTC   3064
TCCGTGGTTC TCACCCCATA CTCTGTCACT GCCACATTTT CACCTGGGCC TGGCCTTTGT   3124
CTCCACCTGA AACTCCTGAA AATCTTGAAA TGGATTTCTA GGTCACTGGG GACTCCGGCA   3184
GCACATTCGG CTTCAGAATA AAGGGCGCCC GCGGTCCCCC AGCACCTCCC CAAGCCACAC   3244
CCCTAGCTTC CCTCCCTATC CCTGCAGCCT GAGGGTCCCT TCAGCCACCC TTAAGTCCCC   3304
ACCTGGGCTC CTGCCCCGCC CCTGGCTAGC AGCGCCTTCT CCACCGGGGC CCCCTCTGCT   3364
CACAGAGCCC CCTCACCTCC CTGGGGATGA GGGGCCAGGC CATGACCCTG AAAGTCTAGC   3424
CCTGGCCTTG ACCTCCCAGG AGCGCCCTCC CCGCCCTCTC CCGGCCCCGG CCCCGTCCTC   3484
TGCTGCTGGC CTCTGGGTCG TGCCCCGCAG ACTGAGCTGC GCTTGGGGGT CCTGGCGGCC   3544
TGGGCCGTCC CGCACCGAAC CCAGGCGGTC GGAGCCCGGC GGGAAGGCGC GAGGTCCTTC   3604
TGGGGGCTCC TCCGACGCCT GAGGGCGCTG CTTCCCCGCG GCCGCCCCGG GTTTCTGCGG   3664
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AGCCGGGGCC TCCGCTCTCG GGTGACCCGG TGAGACCCCC GGGGAGGCCG CTGGGGAGGC 3724
GCGGGCTCTG CTCCCGGGTC CCAAACGCAC TGGCTGCCCC TCAGGAGGGA CGGCGACCTC 3784
CACCCACGGC GCTGGCGCCC GCACGGCCGC TCCTCCCGCT CCCGCAGCCT GGACGCCTCC 3844
CGAGGCCGCC CCGCCGGGCC CCACGCGCGG CCCCATCCGC AGGCCAGGAC TGCCTTCCCG 3904
GAGCTGGCGG CCCCCAGCCT GGAGGAGCCG GCCCCAGACG CCCTCCCAGC CCTCCCCAGC 3964
CCACTCTGGC CCCGCAGCCC CCGCCTGGTC CGAGTGCGGG TCTCTGGCCC CGGCCTTTCC 4024
CGGGGAAGGA AAGCAAAAAG CTT 4047

(2) INFORMATION FOR SEQ ID NO:148:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 474 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:

Met Asn Gly Asp Met Pro His Val Pro Ile Thr Thr Leu Ala Gly Ile
1 5 10 15
Ala Ser Leu Thr Asp Leu Leu Asn Gln Leu Pro Leu Pro Ser Pro Leu
20 25 30
Pro Ala Thr Thr Thr Lys Ser Leu Leu Phe Asn Ala Arg Ile Ala Glu
35 40 45
Glu Val Asn Cys Leu Leu Ala Cys Arg Asp Asp Asn Leu Val Ser Gln
50 55 60
Leu Val His Ser Leu Asn Gln Val Ser Thr Asp His Ile Glu Leu Lys
65 70 75 80
Asp Asn Leu Gly Ser Asp Asp Pro Glu Gly Asp Ile Pro Val Leu Leu
85 90 95
Gln Ala Val Leu Ala Arg Ser Pro Asn Val Phe Arg Glu Lys Ser Met
100 105 110
Gln Asn Arg Tyr Val Gln Ser Gly Met Met Met Ser Gln Tyr Lys Leu
115 120 125
Ser Gln Asn Ser Met His Ser Ser Pro Ala Ser Ser Asn Tyr Gln Gln
130 135 140
Thr Thr Ile Ser His Ser Pro Ser Ser Arg Phe Val Pro Pro Gln Thr
145 150 155 160
Ser Ser Gly Asn Arg Phe Met Pro Gln Gln Asn Ser Pro Val Pro Ser
165 170 175
Pro Tyr Ala Pro Gln Ser Pro Ala Gly Tyr Met Pro Tyr Ser His Pro
180 185 190
Ser Ser Tyr Thr Thr His Pro Gln Met Gln Gln Ala Ser Val Ser Ser
195 200 205
Pro Ile Val Ala Gly Gly Leu Arg Asn Ile His Asp Asn Lys Val Ser
210 215 220
Gly Pro Leu Ser Gly Asn Ser Ala Asn His His Ala Asp Asn Pro Arg
225 230 235 240
His Gly Ser Ser Glu Asp Tyr Leu His Met Val His Arg Leu Ser Ser
245 250 255
Asp Asp Gly Asp Ser Ser Thr Met Arg Asn Ala Ala Ser Phe Pro Leu
260 265 270
Arg Ser Pro Gln Pro Val Cys Ser Pro Ala Gly Ser Glu Gly Thr Pro
275 280 285

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Lys Gly Ser Arg Pro Pro Leu Ile Leu Gln Ser Gln Ser Leu Pro Cys
    290                 295                 300
Ser Ser Pro Arg Asp Val Pro Pro Asp Ile Leu Leu Asp Ser Pro Glu
305                 310                 315                 320
Arg Lys Gln Lys Lys Gln Lys Lys Met Lys Leu Gly Lys Asp Glu Lys
                325                 330                 335
Glu Gln Ser Glu Lys Ala Ala Met Tyr Asp Ile Ile Ser Ser Pro Ser
            340                 345                 350
Lys Asp Ser Thr Lys Leu Thr Leu Arg Leu Ser Arg Val Arg Ser Ser
        355                 360                 365
Asp Met Asp Gln Gln Glu Asp Met Ile Ser Gly Val Glu Asn Ser Asn
    370                 375                 380
Val Ser Glu Asn Asp Ile Pro Phe Asn Val Gln Tyr Pro Gly Gln Thr
385                 390                 395                 400
Ser Lys Thr Pro Ile Thr Pro Gln Asp Ile Asn Arg Pro Leu Asn Ala
                405                 410                 415
Ala Gln Cys Leu Ser Gln Gln Glu Gln Thr Ala Phe Leu Pro Ala Asn
            420                 425                 430
Gln Val Pro Val Leu Gln Gln Asn Thr Ser Val Ala Ala Lys Gln Pro
        435                 440                 445
Gln Thr Asn Ser His Lys Thr Leu Val Gln Pro Gly Thr Gly Ile Glu
    450                 455                 460
Val Ser Ala Glu Leu Pro Lys Asp Lys Thr
465                 470
```

(2) INFORMATION FOR SEQ ID NO:149:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2998 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 26...799
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:149:

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AAGCTTTTTG AATTCGGCAC GAGAT GCT ACA CAG GCT ATA TTT GAA ATA CTG      52
                               Ala Thr Gln Ala Ile Phe Glu Ile Leu
                                1               5

GAG AAA TCC TGG TTG CCC CAG AAT TGT ACA CTG GTT GAT ATG AAG ATT     100
Glu Lys Ser Trp Leu Pro Gln Asn Cys Thr Leu Val Asp Met Lys Ile
10                  15                  20                  25

GAA TTT GGT GTT GAT GTA ACC ACC AAA GAA ATT GTT CTT GCT GAT GTT     148
Glu Phe Gly Val Asp Val Thr Thr Lys Glu Ile Val Leu Ala Asp Val
                30                  35                  40

ATT GAC AAT GAT TCC TGG AGA CTC TGG CCA TCA GGA GAT CGA AGC CAA     196
Ile Asp Asn Asp Ser Trp Arg Leu Trp Pro Ser Gly Asp Arg Ser Gln
            45                  50                  55
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CAG AAA GAC AAA CAG TCT TAT CGG GAC CTC AAA GAA GTA ACT CCT GAA      244
Gln Lys Asp Lys Gln Ser Tyr Arg Asp Leu Lys Glu Val Thr Pro Glu
        60                  65                  70

GGG CTC CAA ATG GTA AAG AAA AAC TTT GAG TGG GTT GCA GAG AGA GTA      292
Gly Leu Gln Met Val Lys Lys Asn Phe Glu Trp Val Ala Glu Arg Val
    75                  80                  85

GAG TTG CTT TTG AAA TCA GAA AGT CAG TGC AGG GTT GTA GTG TTG ATG      340
Glu Leu Leu Leu Lys Ser Glu Ser Gln Cys Arg Val Val Val Leu Met
90                  95                  100                 105

GGC TCT ACT TCT GAT CTT GGT CAC TGT GAA AAA ATC AAG AAG GCC TGT      388
Gly Ser Thr Ser Asp Leu Gly His Cys Glu Lys Ile Lys Lys Ala Cys
                110                 115                 120

GGA AAT TTT GGC ATT CCA TGT GAA CTT CGA GTA ACA TCT GCG CAT AAA      436
Gly Asn Phe Gly Ile Pro Cys Glu Leu Arg Val Thr Ser Ala His Lys
            125                 130                 135

GGA CCA GAT GAA ACT CTG AGG ATT AAA GCT GAG TAT GAA GGG GAT GGC      484
Gly Pro Asp Glu Thr Leu Arg Ile Lys Ala Glu Tyr Glu Gly Asp Gly
        140                 145                 150

ATT CCT ACT GTA TTT GTG GCA GTG GCA GGC AGA AGT AAT GGT TTG GGA      532
Ile Pro Thr Val Phe Val Ala Val Ala Gly Arg Ser Asn Gly Leu Gly
    155                 160                 165

CCA GTG ATG TCT GGG AAC ACT GCA TAT CCA GTT ATC AGC TGT CCT CCC      580
Pro Val Met Ser Gly Asn Thr Ala Tyr Pro Val Ile Ser Cys Pro Pro
170                 175                 180                 185

CTC ACA CCA GAC TGG GGA GTT CAG GAT GTG TGG TCT TCT CTT CGA CTA      628
Leu Thr Pro Asp Trp Gly Val Gln Asp Val Trp Ser Ser Leu Arg Leu
                190                 195                 200

CCC AGT GGT CTT GGC TGT TCA ACC GTA CTT TCT CCA GAA GGA TCA GCT      676
Pro Ser Gly Leu Gly Cys Ser Thr Val Leu Ser Pro Glu Gly Ser Ala
            205                 210                 215

CAA TTT GCT GCT CAG ATA TTT GGG TTA AGC AAC CAT TTG GTA TGG AGC      724
Gln Phe Ala Ala Gln Ile Phe Gly Leu Ser Asn His Leu Val Trp Ser
        220                 225                 230

AAA CTG CGA GCA AGC ATT TTG AAC ACA TGG ATT TCC TTG AAG CAG GCT      772
Lys Leu Arg Ala Ser Ile Leu Asn Thr Trp Ile Ser Leu Lys Gln Ala
    235                 240                 245

GAC AAG AAA ATC AGA GAA TGT AAT TTA TAAGAAAGAA TGCCATTGAA TTTTTTA    826
Asp Lys Lys Ile Arg Glu Cys Asn Leu
250                 255

GGGGAAAAAC TACAAATTTC TAATTTAGCT GAAGGAAAAT CAAGCAAGAT GAAAAGGTAA    886
TTTTAAATTA GAGAACACAA ATAAAATGTA TTAGTGAATA AATGGTGAGG GTAGGCCTAT    946
TCAGATGCAA GGCCAGCAAT GGGGCTCCCC ATTATCCCCA CCCCTTTGGT CCCAGTCCCC   1006
TTCTCTGCAA TGGGCACGCA TAGAGGAGAG ACAAAGGGTA TTAGACGCAA CATCATTGGC   1066
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CCAGGGGAGT CCGAGAAGAG CTGCCATTGG CTGACAGGGC ATTTTCAGGC TCTGTCATTG 1126
GTCAGGGAGC ACACCCCAGC CTGAAGAGTG ATGCCATTGG CCAGGGAGTG GTTTTGTCAT 1186
AGCCGTTGGC TGTGAAGTGG AAGGAAAAGA TCTGGGAATG AAGCCCTGTG GCCAGGAAGA 1246
TAGACAGGGC AGCAACTTCT GGGCCTCCAG GCCCTCTTCC CACCATAGCA ATGTGGGCAA 1306
AACTGGTGTC AGGCCCCAGC CAGAAAAAGG AGCCCAAGCC AGAGGGCAAG TGACAAAGGA 1366
TGTACCATGT CCAATCTCCC ACACCCTGGG GCTGCCCTTC CCAATGTCTT TCTTGATAGC 1426
CAAGTTGGGC TGGGAGCAGC TCACTGCTCC TCTAGCCAGG AGGGTTTCTC AGCTCCTGGA 1486
GGCCGCAGCT TGATGTTGAA CTGCTGCAGG GTCTGCTCCA GCTGTTTCTG GTTCCCAGCA 1546
AAGTAGGCGG ACACAGCATT GTGGAAGAGC AGCAGCTGCT TGTGCATCAC CTTGATCTTG 1606
TTTTCTTCCA GGAACTTGAG CTTGATGGCC ACATCTCCCC GCAGCTTCTC ATACTTGTCC 1666
CGATGGGCCT GGAAAGTGGC CTGGGCACTC TCAAGTCGAC CACGTGTCCC TGCATCCCGG 1726
GGGCCTAGAC TCAGCTCCTC TAAGTCTGTT CGGTAGGCAT CATATTCCAG CCTGGCAGCC 1786
TCATACTGTT TCACAGTCAT GAGCGTGTCT TCCATGGTCT TGGTGACCAA TGTGTTGATG 1846
CTAGAGACAA AGAAGTTCAC GGCTCCTAGC AGCGTTTCCC CATTCTTGCA TAGTAGTTTC 1906
TGTGTCTCTG CATTGTAGCC AAATTCCTCC TGAAGCTCTG GGGACTTCTG GCTGAGGTCA 1966
GCAAAGGCAT CACCCAGTGC ATGCTGGGTC TGCAGCAGGC TGTAGAGGTG GGCTGTCAGT 2026
GCCCGGCCCA GCTGCAGGAC ACTCTCATAC TTGCGCTTCG TCTCACGCAG CAACTCAATC 2086
TGCAGCTCTA GCTCCAGGAT TCCGGCGCCT CCACTCCGTC CCCCGCGGGT CTGCTCTGTG 2146
TGCCATGGAC GGCATTGTCC CAGATATAGC CGTTGGTACA AAGCGGGGAT CTGACGAGCT 2206
TTTCTCTACT TGTGTCACTA ACGGACCGTT TATCATGAGC AGCAACTCGG CTTCTGCAGC 2266
AAACGGAAAT GACAGCAAGA AGTTCAAAGG TGACAGCCGA AGTGCAGGCG TCCCCTCTAG 2326
AGTGATCCAC ATCCGGAAGC TCCCCATCGA CGTCACGGAG GGGGAAGTCA TCTCCCTGGG 2386
GCTGCCCTTT GGGAAGGTCA CCAACCTCCT GATGCTGAAG GGGAAAAACC AGGCCTTCAT 2446
CGAGATGAAC ACGGAGGAGG CTGCCAATAC CATGGTGAAC TACTACACCT CGGTGACCCC 2506
TGTGCTGCGC GGCCAGCCCA TCTACATCCA GTTCTCCAAC CACAAGGAGC TGAAGACCGA 2566
CAGCTCTCCC AACCAGGCGC GGGCCCAGGC GGCCCTGCAG GCGGTGAACT CGGTCCAGTC 2626
GGGGAACCTG GCCTTGGCTG CCTCGGCGGC GGCCGTGGAT GCAGGGATGG CGATGGCCGG 2686
GCAGAGCCCC GTGCTCAGGA TCATCGTGGA GAACCTCTTC TACCCTGTGA CCCTGGATGT 2746
GCTGCACCAG ATTTTCTCCA AGTTCGGCAC AGTGTTGAAG ATCATCACCT TCACCAAGAA 2806
CAACCAGTTC CAGGCCCTGC TGCAGTATGC GGACCCCGTG AGCGCCCAGC ACGCCAAGCT 2866
GTCGCTGGAC GGGCAGAACA TCTACAACGC CTGCTGCACG CTGCGCATCG ACTTTTCCAA 2926
GCTCACCAGC CTCAACGTCA AGTACAACAA TGACAAGAGC CGTGACTACC TCGTGCCGAA 2986
TTCTTTGGAT CC 2998

(2) INFORMATION FOR SEQ ID NO:150:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 258 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:

Ala Thr Gln Ala Ile Phe Glu Ile Leu Glu Lys Ser Trp Leu Pro Gln
1 5 10 15
Asn Cys Thr Leu Val Asp Met Lys Ile Glu Phe Gly Val Asp Val Thr
20 25 30
Thr Lys Glu Ile Val Leu Ala Asp Val Ile Asp Asn Asp Ser Trp Arg
35 40 45
Leu Trp Pro Ser Gly Asp Arg Ser Gln Gln Lys Asp Lys Gln Ser Tyr
50 55 60
Arg Asp Leu Lys Glu Val Thr Pro Glu Gly Leu Gln Met Val Lys Lys
65 70 75 80

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Asn Phe Glu Trp Val Ala Glu Arg Val Glu Leu Leu Leu Lys Ser Glu
                85                  90                  95
Ser Gln Cys Arg Val Val Val Leu Met Gly Ser Thr Ser Asp Leu Gly
            100                 105                 110
His Cys Glu Lys Ile Lys Lys Ala Cys Gly Asn Phe Gly Ile Pro Cys
        115                 120                 125
Glu Leu Arg Val Thr Ser Ala His Lys Gly Pro Asp Glu Thr Leu Arg
    130                 135                 140
Ile Lys Ala Glu Tyr Glu Gly Asp Gly Ile Pro Thr Val Phe Val Ala
145                 150                 155                 160
Val Ala Gly Arg Ser Asn Gly Leu Gly Pro Val Met Ser Gly Asn Thr
                165                 170                 175
Ala Tyr Pro Val Ile Ser Cys Pro Pro Leu Thr Pro Asp Trp Gly Val
            180                 185                 190
Gln Asp Val Trp Ser Ser Leu Arg Leu Pro Ser Gly Leu Gly Cys Ser
        195                 200                 205
Thr Val Leu Ser Pro Glu Gly Ser Ala Gln Phe Ala Ala Gln Ile Phe
    210                 215                 220
Gly Leu Ser Asn His Leu Val Trp Ser Lys Leu Arg Ala Ser Ile Leu
225                 230                 235                 240
Asn Thr Trp Ile Ser Leu Lys Gln Ala Asp Lys Lys Ile Arg Glu Cys
                245                 250                 255
Asn Leu
```

(2) INFORMATION FOR SEQ ID NO:151:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1038 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:

```
Ile Gln Arg Phe Gly Thr Ser Gly His Ile Met Asn Leu Gln Ala Gln
 1               5                  10                  15
Pro Lys Ala Gln Asn Lys Arg Lys Arg Cys Leu Phe Gly Gly Gln Glu
            20                  25                  30
Pro Ala Pro Lys Glu Gln Pro Pro Pro Leu Gln Pro Pro Gln Gln Ser
        35                  40                  45
Ile Arg Val Lys Glu Glu Gln Tyr Leu Gly His Glu Gly Pro Gly Gly
    50                  55                  60
Ala Val Ser Thr Ser Gln Pro Val Glu Leu Pro Pro Pro Ser Ser Leu
65                  70                  75                  80
Ala Leu Leu Asn Ser Val Val Tyr Gly Pro Glu Arg Thr Ser Ala Ala
                85                  90                  95
Met Leu Ser Gln Gln Val Ala Ser Val Lys Trp Pro Asn Ser Val Met
            100                 105                 110
Ala Pro Gly Arg Gly Pro Glu Arg Gly Gly Gly Gly Gly Val Ser Asp
        115                 120                 125
Ser Ser Trp Gln Gln Gln Pro Gly Gln Pro Pro Pro His Ser Thr Trp
    130                 135                 140
Asn Cys His Ser Leu Ser Leu Tyr Ser Ala Thr Lys Gly Ser Pro His
145                 150                 155                 160
Pro Gly Val Gly Val Pro Thr Tyr Tyr Asn His Pro Glu Ala Leu Lys
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                   165                 170                 175
Arg Glu Lys Ala Gly Gly Pro Gln Leu Asp Arg Tyr Val Arg Pro Met
               180                 185                 190
Met Pro Gln Lys Val Gln Leu Glu Val Gly Arg Pro Gln Ala Pro Leu
           195                 200                 205
Asn Ser Phe His Ala Ala Lys Lys Pro Pro Asn Gln Ser Leu Pro Leu
       210                 215                 220
Gln Pro Phe Gln Leu Ala Phe Gly His Gln Val Asn Arg Gln Val Phe
225                 230                 235                 240
Arg Gln Gly Pro Pro Pro Pro Asn Pro Val Ala Ala Phe Pro Pro Gln
                   245                 250                 255
Lys Gln Gln Gln Gln Gln Gln Pro Gln Gln Gln Gln Gln Gln Gln Gln
               260                 265                 270
Ala Ala Leu Pro Gln Met Pro Leu Phe Glu Asn Phe Tyr Ser Met Pro
           275                 280                 285
Gln Gln Pro Ser Gln Gln Pro Gln Asp Phe Gly Leu Gln Pro Ala Gly
       290                 295                 300
Pro Leu Gly Gln Ser His Leu Ala His His Ser Met Ala Pro Tyr Pro
305                 310                 315                 320
Phe Pro Pro Asn Pro Asp Met Asn Pro Glu Leu Arg Lys Ala Leu Leu
                   325                 330                 335
Gln Asp Ser Ala Pro Gln Pro Ala Leu Pro Gln Val Gln Ile Pro Phe
               340                 345                 350
Pro Arg Arg Ser Arg Arg Leu Ser Lys Glu Gly Ile Leu Pro Pro Ser
           355                 360                 365
Ala Leu Asp Gly Ala Gly Thr Gln Pro Gly Gln Glu Ala Thr Gly Asn
       370                 375                 380
Leu Phe Leu His His Trp Pro Leu Gln Gln Pro Pro Pro Gly Ser Leu
385                 390                 395                 400
Gly Gln Pro His Pro Glu Ala Leu Gly Phe Pro Leu Glu Leu Arg Glu
                   405                 410                 415
Ser Gln Leu Leu Pro Asp Gly Glu Arg Leu Ala Pro Asn Gly Arg Glu
               420                 425                 430
Arg Glu Ala Pro Ala Met Gly Ser Glu Glu Gly Met Arg Ala Val Ser
           435                 440                 445
Thr Gly Asp Cys Gly Gln Val Leu Arg Gly Gly Val Ile Gln Ser Thr
       450                 455                 460
Arg Arg Arg Arg Arg Ala Ser Gln Glu Ala Asn Leu Leu Thr Leu Ala
465                 470                 475                 480
Gln Lys Ala Val Glu Leu Ala Ser Leu Gln Asn Ala Lys Asp Gly Ser
                   485                 490                 495
Gly Ser Glu Glu Lys Arg Lys Ser Val Leu Ala Ser Thr Thr Lys Cys
               500                 505                 510
Gly Val Glu Phe Ser Glu Pro Ser Leu Ala Thr Lys Arg Ala Arg Glu
           515                 520                 525
Asp Ser Gly Met Val Pro Leu Ile Ile Pro Val Ser Val Pro Val Arg
       530                 535                 540
Thr Val Asp Pro Thr Glu Ala Ala Gln Ala Gly Gly Leu Asp Glu Asp
545                 550                 555                 560
Gly Lys Gly Leu Glu Gln Asn Pro Ala Glu His Lys Pro Ser Val Ile
                   565                 570                 575
Val Thr Arg Arg Arg Ser Thr Arg Ile Pro Gly Thr Asp Ala Gln Ala
               580                 585                 590
Gln Ala Glu Asp Met Asn Val Lys Leu Glu Gly Glu Pro Ser Val Arg
           595                 600                 605
Lys Pro Lys Gln Arg Pro Arg Pro Glu Pro Leu Ile Ile Pro Thr Lys
       610                 615                 620
```

Ala Gly Thr Phe Ile Ala Pro Pro Val Tyr Ser Asn Ile Thr Pro Tyr
625 630 635 640
Gln Ser His Leu Arg Ser Pro Val Arg Leu Ala Asp His Pro Ser Glu
645 650 655
Arg Ser Phe Glu Leu Pro Pro Tyr Thr Pro Pro Pro Ile Leu Ser Pro
660 665 670
Val Arg Glu Gly Ser Gly Leu Tyr Phe Asn Ala Ile Ile Ser Thr Ser
675 680 685
Thr Ile Pro Ala Pro Pro Pro Ile Thr Pro Lys Ser Ala His Arg Thr
690 695 700
Leu Leu Arg Thr Asn Ser Ala Glu Val Thr Pro Pro Val Leu Ser Val
705 710 715 720
Met Gly Glu Ala Thr Pro Val Ser Ile Glu Pro Arg Ile Asn Val Gly
725 730 735
Ser Arg Phe Gln Ala Glu Ile Pro Leu Met Arg Asp Arg Ala Leu Ala
740 745 750
Ala Ala Asp Pro His Lys Ala Asp Leu Val Trp Gln Pro Trp Glu Asp
755 760 765
Leu Glu Ser Ser Arg Glu Lys Gln Arg Gln Val Glu Asp Leu Leu Thr
770 775 780
Ala Ala Cys Ser Ser Ile Phe Pro Gly Ala Gly Thr Asn Gln Glu Leu
785 790 795 800
Ala Leu His Cys Leu His Glu Ser Arg Gly Asp Ile Leu Glu Thr Leu
805 810 815
Asn Lys Leu Leu Leu Lys Lys Pro Leu Arg Pro His Asn His Pro Leu
820 825 830
Ala Thr Tyr His Tyr Thr Gly Ser Asp Gln Trp Lys Met Ala Glu Arg
835 840 845
Lys Leu Phe Asn Lys Gly Ile Ala Ile Tyr Lys Lys Asp Phe Phe Leu
850 855 860
Val Gln Lys Leu Ile Gln Thr Lys Thr Val Ala Gln Cys Val Glu Phe
865 870 875 880
Tyr Tyr Thr Tyr Lys Lys Gln Val Lys Ile Gly Arg Asn Gly Thr Leu
885 890 895
Thr Phe Gly Asp Val Asp Thr Ser Asp Glu Lys Ser Ala Gln Glu Glu
900 905 910
Val Glu Val Asp Ile Lys Thr Ser Gln Lys Phe Pro Arg Val Pro Leu
915 920 925
Pro Arg Arg Glu Ser Pro Ser Glu Glu Arg Leu Glu Pro Lys Arg Glu
930 935 940
Val Lys Glu Pro Arg Lys Glu Gly Glu Glu Glu Val Pro Glu Ile Gln
945 950 955 960
Glu Lys Glu Glu Gln Glu Glu Gly Arg Glu Arg Ser Arg Arg Ala Ala
965 970 975
Ala Val Lys Ala Thr Gln Thr Leu Gln Ala Asn Glu Ser Ala Ser Asp
980 985 990
Ile Leu Ile Leu Arg Ser His Glu Ser Asn Ala Pro Gly Ser Ala Gly
995 1000 1005
Gly Gln Ala Ser Glu Lys Pro Arg Glu Gly Thr Gly Lys Ser Arg Arg
1010 1015 1020
Ala Leu Pro Phe Ser Glu Lys Lys Lys Lys Lys Gln Lys Ala
1025 1030 1035

(2) INFORMATION FOR SEQ ID NO:152:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 849 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:152:

```
Ile Arg His Glu Val Ser Phe Leu Trp Asn Thr Glu Ala Ala Cys Pro
 1               5                  10                  15
Ile Gln Thr Thr Thr Asp Thr Asp Gln Ala Cys Ser Ile Arg Asp Pro
            20                  25                  30
Asn Ser Gly Phe Val Phe Asn Leu Asn Pro Leu Asn Ser Ser Gln Gly
        35                  40                  45
Tyr Asn Val Ser Gly Ile Gly Lys Ile Phe Met Phe Asn Val Cys Gly
    50                  55                  60
Thr Met Pro Val Cys Gly Thr Ile Leu Gly Lys Pro Ala Ser Gly Cys
65                  70                  75                  80
Glu Ala Glu Thr Gln Thr Glu Glu Leu Lys Asn Trp Lys Pro Ala Arg
                85                  90                  95
Pro Val Gly Ile Glu Lys Ser Leu Gln Leu Ser Thr Glu Gly Phe Ile
            100                 105                 110
Thr Leu Thr Tyr Lys Gly Pro Leu Ser Ala Lys Gly Thr Ala Asp Ala
        115                 120                 125
Phe Ile Val Arg Phe Val Cys Asn Asp Asp Val Tyr Ser Gly Pro Leu
    130                 135                 140
Lys Phe Leu His Gln Asp Ile Asp Ser Gly Gln Gly Ile Arg Asn Thr
145                 150                 155                 160
Tyr Phe Glu Phe Glu Thr Ala Leu Ala Cys Val Pro Ser Pro Val Asp
                165                 170                 175
Cys Gln Val Thr Asp Leu Ala Gly Asn Glu Tyr Asp Leu Thr Gly Leu
            180                 185                 190
Ser Thr Val Arg Lys Pro Trp Thr Ala Val Asp Thr Ser Val Asp Gly
        195                 200                 205
Arg Lys Arg Thr Phe Tyr Leu Ser Val Cys Asn Pro Leu Pro Tyr Ile
    210                 215                 220
Pro Gly Cys Gln Gly Ser Ala Val Gly Ser Cys Leu Val Ser Glu Gly
225                 230                 235                 240
Asn Ser Trp Asn Leu Gly Val Val Gln Met Ser Pro Gln Ala Ala Ala
                245                 250                 255
Asn Gly Ser Leu Ser Ile Met Tyr Val Asn Gly Asp Lys Cys Gly Asn
            260                 265                 270
Gln Arg Phe Ser Thr Arg Ile Thr Phe Glu Cys Ala Gln Ile Ser Gly
        275                 280                 285
Ser Pro Ala Phe Gln Leu Gln Asp Gly Cys Glu Tyr Val Phe Ile Trp
    290                 295                 300
Arg Thr Val Glu Ala Cys Pro Val Val Arg Val Glu Gly Asp Asn Cys
305                 310                 315                 320
Glu Val Lys Asp Pro Arg His Gly Asn Leu Tyr Asp Leu Lys Pro Leu
                325                 330                 335
Gly Leu Asn Asp Thr Ile Val Ser Ala Gly Glu Tyr Thr Tyr Tyr Phe
            340                 345                 350
Arg Val Cys Gly Lys Leu Ser Ser Asp Val Cys Pro Thr Ser Asp Lys
        355                 360                 365
Ser Lys Val Val Ser Ser Cys Gln Glu Lys Arg Glu Pro Gln Gly Phe
    370                 375                 380
His Lys Val Ala Gly Leu Leu Thr Gln Lys Leu Thr Tyr Glu Asn Gly
385                 390                 395                 400
```

Leu Leu Lys Met Asn Phe Thr Gly Gly Asp Thr Cys His Lys Val Tyr
405 410 415
Gln Arg Ser Thr Ala Ile Phe Phe Tyr Cys Asp Arg Gly Thr Gln Arg
420 425 430
Pro Val Phe Leu Lys Glu Thr Ser Asp Cys Ser Tyr Leu Phe Glu Trp
435 440 445
Arg Thr Gln Tyr Ala Cys Pro Pro Phe Asp Leu Thr Glu Cys Ser Phe
450 455 460
Lys Asp Gly Ala Gly Asn Ser Phe Asp Leu Ser Ser Leu Ser Arg Tyr
465 470 475 480
Ser Asp Asn Trp Glu Ala Ile Thr Gly Thr Gly Asp Pro Glu His Tyr
485 490 495
Leu Ile Asn Val Cys Lys Ser Leu Ala Pro Gln Ala Gly Thr Glu Pro
500 505 510
Cys Pro Pro Glu Ala Ala Ala Cys Leu Leu Gly Gly Ser Lys Pro Val
515 520 525
Asn Leu Gly Arg Val Arg Asp Gly Pro Gln Trp Arg Asp Gly Ile Ile
530 535 540
Val Leu Lys Tyr Val Asp Gly Asp Leu Cys Pro Asp Gly Ile Arg Lys
545 550 555 560
Lys Ser Thr Thr Ile Arg Phe Thr Cys Ser Glu Ser Gln Val Asn Ser
565 570 575
Arg Pro Met Phe Ile Ser Ala Val Glu Asp Cys Glu Tyr Thr Phe Ala
580 585 590
Trp Pro Thr Ala Thr Ala Cys Pro Met Lys Ser Asn Glu His Asp Asp
595 600 605
Cys Gln Val Thr Asn Pro Ser Thr Gly His Leu Phe Asp Leu Ser Ser
610 615 620
Leu Ser Gly Arg Ala Gly Phe Thr Ala Ala Tyr Ser Glu Lys Gly Leu
625 630 635 640
Val Tyr Met Ser Ile Cys Gly Glu Asn Glu Asn Cys Pro Pro Gly Val
645 650 655
Gly Ala Cys Phe Gly Gln Thr Arg Ile Ser Val Gly Lys Ala Asn Lys
660 665 670
Arg Leu Arg Tyr Val Asp Gln Val Leu Gln Leu Val Tyr Lys Asp Gly
675 680 685
Ser Pro Cys Pro Ser Lys Ser Gly Leu Ser Tyr Lys Ser Val Ile Ser
690 695 700
Phe Val Cys Arg Pro Glu Ala Gly Pro Thr Asn Arg Pro Met Leu Ile
705 710 715 720
Ser Leu Asp Lys Gln Thr Cys Thr Leu Phe Phe Ser Trp His Thr Pro
725 730 735
Leu Ala Cys Glu Gln Ala Thr Glu Cys Ser Val Arg Asn Gly Ser Ser
740 745 750
Ile Val Asp Leu Ser Pro Leu Ile His Arg Thr Gly Gly Tyr Glu Ala
755 760 765
Tyr Asp Glu Ser Glu Asp Asp Ala Ser Asp Thr Asn Pro Asp Phe Tyr
770 775 780
Ile Asn Ile Cys Gln Pro Leu Asn Pro Met His Gly Val Pro Cys Pro
785 790 795 800
Ala Gly Ala Ala Val Cys Lys Val Pro Ile Asp Gly Pro Pro Ile Asp
805 810 815
Ile Gly Arg Val Ala Gly Pro Pro Ile Leu Asn Pro Ile Ala Asn Glu
820 825 830
Ile Tyr Leu Asn Phe Glu Ser Ser Thr Pro Cys Gln Glu Phe Ser Cys
835 840 845
Lys

(2) INFORMATION FOR SEQ ID NO:153:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 852 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:153:

```
Met Ala Arg Leu Ser Arg Pro Glu Arg Pro Asp Leu Val Phe Glu Glu
 1               5                  10                  15
Glu Asp Leu Pro Tyr Glu Glu Glu Ile Met Arg Asn Gln Phe Ser Val
            20                  25                  30
Lys Cys Trp Leu His Tyr Ile Glu Phe Lys Gln Gly Ala Pro Lys Pro
        35                  40                  45
Arg Leu Asn Gln Leu Tyr Glu Arg Ala Leu Lys Leu Leu Pro Cys Ser
    50                  55                  60
Tyr Lys Leu Trp Tyr Arg Tyr Leu Lys Ala Arg Arg Ala Gln Val Lys
65                  70                  75                  80
His Arg Cys Val Thr Asp Pro Ala Tyr Glu Asp Val Asn Asn Cys His
                85                  90                  95
Glu Arg Ala Phe Val Phe Met His Lys Met Pro Arg Leu Trp Leu Asp
            100                 105                 110
Tyr Cys Gln Phe Leu Met Asp Gln Gly Arg Val Thr His Thr Arg Arg
        115                 120                 125
Thr Phe Asp Arg Ala Leu Arg Ala Leu Pro Ile Thr Gln His Ser Arg
    130                 135                 140
Ile Trp Pro Leu Tyr Leu Arg Phe Leu Arg Ser His Pro Leu Pro Glu
145                 150                 155                 160
Thr Ala Val Arg Gly Tyr Arg Arg Phe Leu Lys Leu Ser Pro Glu Ser
                165                 170                 175
Ala Glu Glu Tyr Ile Glu Tyr Leu Lys Ser Ser Asp Arg Leu Asp Glu
            180                 185                 190
Ala Ala Gln Arg Leu Ala Thr Val Val Asn Asp Glu Arg Phe Val Ser
        195                 200                 205
Lys Ala Gly Lys Ser Asn Tyr Gln Leu Trp His Glu Leu Cys Asp Leu
    210                 215                 220
Ile Ser Gln Asn Pro Asp Lys Val Gln Ser Leu Asn Val Asp Ala Ile
225                 230                 235                 240
Ile Arg Gly Gly Leu Thr Arg Phe Thr Asp Gln Leu Gly Lys Leu Trp
                245                 250                 255
Cys Ser Leu Ala Asp Tyr Tyr Ile Arg Ser Gly His Phe Glu Lys Ala
            260                 265                 270
Arg Asp Val Tyr Glu Glu Ala Ile Arg Thr Val Met Thr Val Arg Asp
        275                 280                 285
Phe Thr Gln Val Phe Asp Ser Tyr Ala Gln Phe Glu Glu Ser Met Ile
    290                 295                 300
Ala Ala Lys Met Glu Thr Ala Ser Glu Leu Gly Arg Glu Glu Glu Asp
305                 310                 315                 320
Asp Val Asp Leu Glu Leu Arg Leu Ala Arg Phe Glu Gln Leu Ile Ser
                325                 330                 335
Arg Arg Pro Leu Leu Leu Asn Ser Val Leu Leu Arg Gln Asn Pro His
            340                 345                 350
```

His Val His Glu Trp His Lys Arg Val Ala Leu His Gln Gly Arg Pro
355 360 365

Arg Glu Ile Ile Asn Thr Tyr Thr Glu Ala Val Gln Thr Val Asp Pro
370 375 380

Phe Lys Ala Thr Gly Lys Pro His Thr Leu Trp Val Ala Phe Ala Lys
385 390 395 400

Phe Tyr Glu Asp Asn Gly Gln Leu Asp Asp Ala Arg Val Ile Leu Glu
405 410 415

Lys Ala Thr Lys Val Asn Phe Lys Gln Val Asp Asp Leu Ala Ser Val
420 425 430

Trp Cys Gln Cys Gly Glu Leu Glu Leu Arg His Glu Asn Tyr Asp Glu
435 440 445

Ala Leu Arg Leu Leu Arg Lys Ala Thr Ala Leu Pro Ala Arg Arg Ala
450 455 460

Glu Tyr Phe Asp Gly Ser Glu Pro Val Gln Asn Arg Val Tyr Lys Ser
465 470 475 480

Leu Lys Val Trp Ser Met Leu Ala Asp Leu Glu Glu Ser Leu Gly Thr
485 490 495

Phe Gln Ser Thr Lys Ala Val Tyr Asp Arg Ile Leu Asp Leu Arg Ile
500 505 510

Ala Thr Pro Gln Ile Val Ile Asn Tyr Ala Met Phe Leu Glu Glu His
515 520 525

Lys Tyr Phe Glu Glu Ser Phe Lys Ala Tyr Glu Arg Gly Ile Ser Leu
530 535 540

Phe Lys Trp Pro Asn Val Ser Asp Ile Trp Ser Thr Tyr Leu Thr Lys
545 550 555 560

Phe Ile Ala Arg Tyr Gly Gly Arg Lys Leu Glu Arg Ala Arg Asp Leu
565 570 575

Phe Glu Gln Ala Leu Asp Gly Cys Pro Pro Lys Tyr Ala Lys Thr Leu
580 585 590

Tyr Leu Leu Tyr Ala Gln Leu Glu Glu Glu Trp Gly Leu Ala Arg His
595 600 605

Ala Met Ala Val Tyr Glu Arg Ala Thr Arg Ala Val Glu Pro Ala Gln
610 615 620

Gln Tyr Asp Met Phe Asn Ile Tyr Ile Lys Arg Ala Ala Glu Ile Tyr
625 630 635 640

Gly Val Thr His Thr Arg Gly Ile Tyr Gln Lys Ala Ile Glu Val Leu
645 650 655

Ser Asp Glu His Ala Arg Glu Met Cys Leu Arg Phe Ala Asp Met Glu
660 665 670

Cys Lys Leu Gly Glu Ile Asp Arg Ala Arg Ala Ile Tyr Ser Phe Cys
675 680 685

Ser Gln Ile Cys Asp Pro Arg Thr Thr Gly Ala Phe Trp Gln Thr Trp
690 695 700

Lys Asp Phe Glu Val Arg His Gly Asn Glu Asp Thr Ile Lys Glu Met
705 710 715 720

Leu Arg Ile Arg Arg Ser Val Gln Ala Thr Tyr Asn Thr Gln Val Asn
725 730 735

Phe Met Ala Ser Gln Met Leu Lys Val Ser Gly Ser Ala Thr Gly Thr
740 745 750

Val Ser Asp Leu Ala Pro Gly Gln Ser Gly Met Asp Asp Met Lys Leu
755 760 765

Leu Glu Gln Arg Ala Glu Gln Leu Ala Ala Glu Ala Glu Arg Asp Gln
770 775 780

Pro Leu Arg Ala Gln Ser Lys Ile Leu Phe Val Arg Ser Asp Ala Ser
785 790 795 800

Arg Glu Glu Leu Ala Glu Leu Ala Gln Gln Val Asn Pro Glu Glu Ile

```
                805                 810                 815
Gln Leu Gly Glu Asp Glu Asp Glu Asp Glu Met Asp Leu Glu Pro Asn
            820                 825                 830
Glu Val Arg Leu Glu Gln Gln Ser Val Pro Ala Ala Val Phe Gly Ser
        835                 840                 845
Leu Lys Glu Asp
    850
```

(2) INFORMATION FOR SEQ ID NO:154:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 693 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:154:

```
Met Phe Ser Ala Leu Lys Lys Leu Val Gly Ser Asp Gln Ala Pro Gly
 1               5                  10                  15
Arg Asp Lys Asn Ile Pro Ala Gly Leu Gln Ser Met Asn Gln Ala Leu
            20                  25                  30
Gln Arg Arg Phe Ala Lys Gly Val Gln Tyr Asn Met Lys Ile Val Ile
        35                  40                  45
Arg Gly Asp Arg Asn Thr Gly Lys Thr Ala Leu Trp His Arg Leu Gln
    50                  55                  60
Gly Arg Pro Phe Val Glu Glu Tyr Ile Pro Thr Gln Glu Ile Gln Val
65                  70                  75                  80
Thr Ser Ile His Trp Ser Tyr Lys Thr Thr Asp Asp Ile Val Lys Val
                85                  90                  95
Glu Val Trp Asp Val Val Asp Lys Gly Lys Cys Lys Lys Arg Gly Asp
            100                 105                 110
Gly Leu Lys Met Glu Asn Asp Pro Gln Glu Xaa Glu Ser Glu Met Ala
        115                 120                 125
Leu Asp Ala Glu Phe Leu Asp Val Tyr Lys Asn Cys Asn Gly Val Val
    130                 135                 140
Met Met Phe Asp Ile Thr Lys Gln Trp Thr Phe Asn Tyr Ile Leu Arg
145                 150                 155                 160
Glu Leu Pro Lys Val Pro Thr His Val Pro Val Cys Val Leu Gly Asn
                165                 170                 175
Tyr Arg Asp Met Gly Glu His Arg Val Ile Leu Pro Asp Asp Val Arg
            180                 185                 190
Asp Phe Ile Asp Asn Leu Asp Arg Pro Pro Gly Ser Ser Tyr Phe Arg
        195                 200                 205
Tyr Ala Glu Ser Ser Met Lys Asn Ser Phe Gly Leu Lys Tyr Leu His
    210                 215                 220
Lys Phe Phe Asn Ile Pro Phe Leu Gln Leu Gln Arg Glu Thr Leu Leu
225                 230                 235                 240
Arg Gln Leu Glu Thr Asn Gln Leu Asp Met Asp Ala Thr Leu Glu Glu
                245                 250                 255
Leu Ser Val Gln Gln Glu Thr Glu Asp Gln Asn Tyr Gly Ile Phe Leu
            260                 265                 270
Glu Met Met Glu Ala Arg Ser Arg Gly His Ala Ser Pro Leu Ala Ala
        275                 280                 285
Asn Gly Gln Ser Pro Ser Pro Gly Ser Gln Ser Pro Val Leu Pro Ala
    290                 295                 300
Pro Ala Val Ser Thr Gly Ser Ser Ser Pro Gly Thr Pro Gln Pro Ala
```

```
305                 310                 315                 320
Pro Gln Leu Pro Leu Asn Ala Ala Pro Pro Ser Ser Val Pro Pro Val
                325                 330                 335
Pro Pro Ser Glu Ala Leu Pro Pro Pro Ala Cys Pro Ser Ala Pro Ala
            340                 345                 350
Pro Arg Arg Ser Ile Ile Ser Arg Leu Phe Gly Thr Ser Pro Ala Thr
        355                 360                 365
Glu Ala Ala Pro Pro Pro Pro Glu Pro Val Pro Ala Ala Gln Gly Pro
    370                 375                 380
Ala Thr Val Gln Ser Val Glu Asp Phe Val Pro Asp Asp Arg Leu Asp
385                 390                 395                 400
Arg Ser Phe Leu Glu Asp Thr Thr Pro Ala Arg Asp Glu Lys Lys Val
                405                 410                 415
Gly Ala Lys Ala Ala Gln Gln Asp Ser Asp Ser Asp Gly Glu Ala Leu
            420                 425                 430
Gly Gly Asn Pro Met Val Ala Gly Phe Gln Asp Asp Val Asp Leu Glu
        435                 440                 445
Asp Gln Pro Arg Gly Ser Pro Pro Leu Pro Ala Gly Pro Val Pro Ser
    450                 455                 460
Gln Asp Ile Thr Leu Ser Ser Glu Glu Glu Ala Glu Val Ala Ala Pro
465                 470                 475                 480
Thr Lys Gly Pro Ala Pro Ala Pro Gln Gln Cys Ser Glu Pro Glu Thr
                485                 490                 495
Lys Trp Ser Ser Ile Pro Ala Ser Lys Pro Arg Arg Gly Thr Ala Pro
            500                 505                 510
Thr Arg Thr Ala Ala Pro Pro Trp Pro Gly Gly Val Ser Val Arg Thr
        515                 520                 525
Gly Pro Glu Lys Arg Ser Ser Thr Arg Pro Pro Ala Glu Met Glu Pro
    530                 535                 540
Gly Lys Gly Glu Gln Ala Ser Ser Ser Glu Ser Asp Pro Glu Gly Pro
545                 550                 555                 560
Ile Ala Ala Gln Met Leu Ser Phe Val Met Asp Asp Pro Asp Phe Glu
                565                 570                 575
Ser Glu Gly Ser Asp Thr Gln Arg Arg Ala Asp Asp Phe Pro Val Arg
            580                 585                 590
Asp Asp Pro Ser Asp Val Thr Asp Glu Asp Glu Gly Pro Ala Glu Pro
        595                 600                 605
Pro Pro Pro Pro Lys Leu Pro Leu Pro Ala Phe Arg Leu Lys Asn Asp
    610                 615                 620
Ser Asp Leu Phe Gly Leu Gly Leu Glu Glu Ala Gly Pro Lys Glu Ser
625                 630                 635                 640
Ser Glu Glu Gly Lys Glu Gly Lys Thr Pro Ser Lys Glu Lys Lys Lys
                645                 650                 655
Lys Thr Lys Ser Phe Ser Arg Val Leu Leu Glu Arg Pro Arg Ala His
            660                 665                 670
Arg Phe Ser Thr Arg Val Gly Tyr Gln Val Ser Val Pro Asn Ser Pro
        675                 680                 685
Tyr Ser Glu Ser Tyr
    690
```